Short Communication

Human Papillomavirus Types by Age in Cervical Cancer Precursors: Predominance of Human Papillomavirus 16 in Young Women

Carolina Porras,[1] Ana Cecilia Rodríguez,[1] Allan Hildesheim,[2] Rolando Herrero,[1] Paula González,[1] Sholom Wacholder,[2] Robert D. Burk,[3] and Mark Schiffman[2]

[1]Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, San José, Costa Rica; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland; and [3]Albert Einstein Cancer Center, Albert Einstein College of Medicine, Bronx, New York

Abstract

In a population-based study conducted in Guanacaste, Costa Rica, we investigated the human papillomavirus (HPV) types detected in 233 cases of cervical intraepithelial neoplasia (CIN) 2/3 and cancer by age. CIN2+ and CIN3+ in young women were significantly more likely to be associated with HPV 16 than the same lesions in older women (80% of CIN3+ were associated with HPV 16 among women ages 18-26 years compared with only 32% among women older than 55 years; P_{trend} = 0.018). There were no differences by age in HPV 18 positivity. Lesions in older women were mainly caused by other carcinogenic types. This association was present for both prevalent and incident lesions and supports the notion that HPV 16 is a stronger carcinogen than other HPV types. It also has implications for prevention, including the need to vaccinate young women before exposure to HPV vaccine–containing types (HPV 16 and HPV 18) to prevent the majority of cervical cancer precursors. (Cancer Epidemiol Biomarkers Prev 2009;18(3):863–5)

Introduction

Persistent infection with carcinogenic human papillomavirus (HPV; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, possibly others) is the necessary cause of cervical cancer (1, 2). HPV 16 and HPV 18 infections have higher absolute risk of progression to precancer than other HPV types (3-5) and account for 70% of cervical cancers despite representing a modest fraction of infections in general population (6, 7). Furthermore, up to 90% of many HPV-associated extracervical tumors are linked to HPV 16, and HPV 18 is overrepresented in cervical adenocarcinomas (8-11).

We hypothesized that, given a high frequency of HPV acquisition early after sexual debut, HPV 16 and HPV 18, being more carcinogenic than other types, should cause precancer and cancer relatively more frequently at younger than at older ages. Understanding these etiologic details has important public health implications and might affect the way health policy groups consider the benefits of prophylactic HPV 16 and HPV 18 vaccination in different age groups and integration of screening using HPV tests.

We evaluated whether HPV 16 and HPV 18 cause cervical intraepithelial neoplasia (CIN)2+ in women at younger ages than other carcinogenic types in our 10049-women population-based natural history study in Guanacaste, Costa Rica (12-14).

Materials and Methods

Briefly, a random sample of homes was ascertained by a census, and all resident women older than 18 y were invited, to ultimately include one sixth of the population. Participation rates were over 93%. All women signed informed consent at enrollment. The protocol was approved by Institutional Review Boards at National Cancer Institute and Costa Rica.

The cohort was intensively screened at enrollment (1993-1994) and followed for 7 y at varying intervals according to identified clinical risk. Participation rates during follow-up approached 90%. At each visit, cervical specimens for screening and HPV detection were collected. Women with abnormalities were referred to colposcopy. Biopsies and/or excisional treatments were done as necessary and the histologic final diagnosis was assigned after review by an expert panel including all available cytology and pathology data.

HPV detection and typing was done using MY09/11 L1 degenerate primer PCR with AmpliTaq Gold polymerase followed by dot blot hybridization detecting >40 HPV types. There was extensive replicate testing in

Received 10/8/08; revised 11/15/08; accepted 12/9/08.

Grant support: The Guanacaste cohort was supported by NIH (contracts numbers NO1-CP-21081, NO1-CP-33061, NO1-CP-40542, NO1-CP-50535, NO1-CP-81023, and CA78527; R.D. Burk). This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Requests for reprints: Carolina Porras, Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, Torre La Sabana, 300 Oeste del ICE, Piso 7, Sabana Norte, San José, Costa Rica. Phone: 506-2665-0242; Fax: 506-2666-3595. E-mail: cporras@proyectoguanacaste.org

doi:10.1158/1055-9965.EPI-08-0951

separate batches, and adjudication of discrepant data blinded to cytology and histology data.

We evaluated the HPV type distribution stratified in 5 age groups (18-26, 27-30, 31-36, 37-45, 46-55, ≥56 y) among women with CIN2+, detected at enrollment or follow-up among nonhysterectomized and sexually experienced women. For analyses focusing on HPV 16 versus other carcinogenic HPV types, if multiple types including HPV 16 were detected at the time of diagnosis, the ''causative'' type was assigned as HPV 16; otherwise, the case was assigned to ''other'' carcinogenic HPV types. Similarly, for analysis that focused on HPV 18, if multiple HPV types were present, the ''causative'' type was assigned as HPV 18; otherwise, to ''other'' carcinogenic HPV types. We also evaluated the HPV type distribution by age restricted to women with single infections ($n = 172$) with similar findings (data not shown). Contingency tables were constructed for all cases and also restricted to incident cases; results are presented separately for CIN2+ and CIN3+. The proportion of lesions associated with HPV types of interest (HPV 16 and HPV 18, respectively) were each evaluated. The trend of HPV 16 positivity across age groups was estimated using Mantel-Haenszel χ^2 (1 degrees of freedom).

Results

At enrollment, we identified 140 women with prevalent CIN2+ among 8,546 sexually experienced women. Among 8,759 women in follow-up (including initially virginal women who initiated sexual activity during follow-up), 141 incident cases were identified. A total of 233 prevalent and incident CIN2+ cases were positive for any carcinogenic HPV type and included in the analyses. Analyses excluding invasive cancers yielded comparable results and are not presented.

Among the CIN2+ cases, 38% were CIN2, 55% were CIN3, and 7% were screening-detected (not by symptoms) invasive cancer. The distribution of lesion severity did not differ by age ($P = 0.787$). Women diagnosed in Guanacaste due to symptoms tended to be substantially older on average than those found at screening.

Among women with incident or prevalent CIN2+ (Table 1), significant differences in the distribution of HPV types were observed by age, with a decline in HPV 16 positivity from 67.6% among women ages 18 to 26 years to 27.6% among women ages ≥56 years and a corresponding increase in positivity for other carcinogenic types ($P_{trend} = 0.002$). Similar results were observed in analyses restricted to incident CIN2+ ($P_{trend} = 0.001$; Table 1) and when restricting to all CIN3+ cases ($P_{trend} = 0.018$) or only incident CIN3+ cases ($P_{trend} = 0.009$; Table 2). The pattern of declining HPV 16 with age was clear, with the exception of an apparent increase at ages 46 to 55 years; however, despite this increase in HPV 16 positivity observed at ages 46 to 55 years, positivity rates were still lower in this age group than those observed among women ages 30 years and younger, particularly in analyses restricted to incident disease. There were no consistent or significant patterns by age for HPV 18 or any other individual type. Of note, over 35% of CIN2+ cases were detected by age 30 years, whereas <24% of our cases were diagnosed at ages above 45 years.

Discussion

HPV 16 is known to cause ~50% of cervical cancers and its precursors, but until now, it was not fully recognized that the fraction of lesions associated with this HPV type is higher among young women. In a large pooled analysis of invasive cervical cancers (1), HPV 16–related cancers were significantly but not markedly more common in younger women, and a recent report documented younger ages for invasive cancers associated with HPV 16, 18, and 45 (15).

Vaccines against HPV 16 and 18 are now being incorporated in prevention programs, and there is discussion about the appropriate ages to vaccinate. It is widely accepted that vaccinating adolescents is the most cost-effective approach for prevention, considering that most HPV infections occur early after initiation of sexual activity. However, some groups advocate vaccinating older women, claiming that exposure and new disease continue to occur into midadulthood. In this analysis, we showed that cervical cancer precursors occurring in younger women are significantly more likely to be associated with HPV 16 than lesions occurring in older women. These findings, together with the fact that the peak of cervical cancer precursors is also relatively early in life clearly indicate that the vaccine benefit will be maximal when given to young women, and that programs aimed at older women will have a reduced effect on the burden of cervical disease. HPV 16 and 18 are considered stronger carcinogens, as shown in laboratory and epidemiologic studies (15-18), and it would

Table 1. HPV types detected among HPV positive women with CIN2+ by age

Age (y)	Incident and prevalent cases ($n = 233$)			Incident cases ($n = 117$)		
	No. women	HPV category* (%)		No. women	HPV category* (%)	
		HPV 16	Other carcinogenic		HPV 16	Other carcinogenic
18-26	37	67.6	32.4	19	68.4	31.6
27-30	45	57.8	42.2	24	62.5	37.5
31-36	48	47.9	52.1	19	47.4	52.6
37-45	49	38.8	61.2	27	25.9	74.1
46-55	25	56.0	44.0	14	35.7	64.3
≥56	29	27.6	72.4	14	28.6	71.4
P_{trend}			0.002			0.001

*Each woman was counted only once: if multiple HPV types were detected including HPV 16, she was counted as HPV 16 positive; otherwise, the woman was assigned to other carcinogenic HPV type.

Table 2. HPV types detected among HPV positive women with CIN3+ by age

Age (y)	Incident and prevalent cases (n = 148)			Incident cases (n = 73)		
	No. women	HPV category* (%)		No. women	HPV category* (%)	
		HPV 16	Other carcinogenic		HPV 16	Other carcinogenic
18-26	24	79.2	20.8	12	83.3	16.7
27-30	25	52.0	48.0	13	53.8	46.2
31-36	29	41.4	58.6	10	40.0	60.0
37-45	31	45.2	54.8	16	31.2	68.8
46-55	20	60.0	40.0	11	45.5	54.5
≥56	19	31.6	68.4	11	27.3	72.7
P_{trend}			0.018			0.009

*Each woman was counted only once: if multiple HPV types were detected including HPV 16, she was counted as HPV 16 positive; otherwise the woman was assigned to other carcinogenic HPV type.

therefore not be surprising if they cause disease earlier. Interestingly, in our study, we did not observe a similar age association for HPV 18, in concordance with previous findings indicating an ''occult'' progression of HPV 18 in the initial years after infection.

A cohort effect could explain our findings if HPV had only recently been introduced in this population, but this is not supported by comparing these data with a more recent cohort recruited 10 years later in the same population (19). HPV 16 is known to produce identifiable high-grade cytologic (20) and colposcopic abnormalities (21) more readily, and increased detectability could partly explain our results. When interpreting these findings, we need to keep in mind that HPV 16–related CIN2 and CIN3 in younger women may be more likely to regress than similar lesions in older women. However, in our study, the association with age remained when restricting to CIN3+, which are less likely to regress.

These analyses need to be replicated for each individual type of HPV in other studies of precursors and invasive disease. A better understanding of age patterns in cervical lesions by HPV types will help inform decisions regarding the ideal target groups for vaccination and screening programs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

We thank the women who participated in this study and the staff for their dedicated work.

References

1. Muñoz N, Bosch FX, de Sanjosé S, et al.; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–27.
2. Cogliano V, Baan R, Straif K, et al.; WHO International Agency for Research on Cancer. Carcinogenicity of human papillomaviruses. Lancet Oncol 2005;6:204.
3. Kjaer S, Høgdall E, Frederiksen K, et al. The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period. Cancer Res 2006;66:10630–6.
4. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst 2005;97:1072–9.
5. Castle PE, Solomon D, Schiffman M, et al. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. J Natl Cancer Inst 2005;97:1066–71.
6. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 2007;121:621–32.
7. Clifford G, Franceschi S, Diaz M, et al. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine 2006;24 Suppl 3:S26–34.
8. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007;356:1944–56.
9. Herrero R, Castellsagué X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 2003;95:1772–83.
10. Bulk S, Berkhof J, Bulkmans NW, et al. Preferential risk of HPV16 for squamous cell carcinoma and of HPV18 for adenocarcinoma of the cervix compared to women with normal cytology in The Netherlands. Br J Cancer 2006;94:171–5.
11. Zielinski GD, Snijders PJ, Rozendaal L, et al. The presence of high-risk HPV combined with specific p53 and p16INK4a expression patterns points to high-risk HPV as the main causative agent for adenocarcinoma *in situ* and adenocarcinoma of the cervix. J Pathol 2003;201:535–43.
12. Herrero R, Schiffman MH, Bratti C, et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste Project. Rev Panam Salud Publica 1997;1:362–75.
13. Bratti MC, Rodríguez AC, Schiffman M, et al. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10000 women in Guanacaste, Costa Rica,. Rev Panam Salud Publica 2004;15:75–89.
14. Herrero R, Castle PE, Schiffman M, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. J Infect Dis 2005;191:1796–807.
15. Vinokurova S, Wentzensen N, Kraus I, et al. Type-dependent integration frequency of human papillomavirus genomes in cervical lesions. Cancer Res 2008;68:307–13.
16. Rodríguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst 2008;100:513–7.
17. Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis 2005;191:731–8.
18. Strickler HD, Palefsky JM, Shah KV, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. J Natl Cancer Inst 2003;95:1062–71.
19. Herrero R, Hildesheim A, Rodríguez AC, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. Vaccine 2008;26:4795–808.
20. Kovacic MB, Castle PE, Herrero R, et al. Relationships of human papillomavirus type, qualitative viral load, and age with cytologic abnormality. Cancer Res 2006;66:10112–9.
21. Massad LS, Jeronimo J, Schiffman M, et al. Interobserver agreement in the assessment of components of colposcopic grading. Obstet Gynecol 2008;111:1279–84.

Human Papillomavirus Types by Age in Cervical Cancer Precursors: Predominance of Human Papillomavirus 16 in Young Women

Carolina Porras, Ana Cecilia Rodríguez, Allan Hildesheim, et al.

Cancer Epidemiol Biomarkers Prev 2009;18:863-865.