Re: Human Papillomavirus Type 16 and 18 Variants: Race-Related Distribution and Persistence

Non-European variants of human papillomaviruses (HPVs) 16 and 18 are associated with increased risk of developing preinvasive cervical lesions (1). In a recent article in the Journal, Xi et al. (2) showed that European and African variants of HPVs 16 and 18 were predominantly detected in white and African American women, respectively. Most importantly, they showed that infections with these variants tend to persist longer in women whose ancestry matches that of the variant’s geographic origin. Race was self-reported by study participants.

Prompted by these compelling findings, we used Kaplan–Meier analysis and log-rank tests to assess the outcomes of prevalent and incident variant-specific infection with HPVs 16 and/or 18 by different racial categories among women from the Ludwig/McGill cohort study conducted in Brazil (3). The subject’s race was inferred by trained nurses during an interview. Race categories were combined for analysis as white and nonwhite, with the latter category being composed mostly of black women or women with visible African–Brazilian ancestry. European variants of HPVs 16 or 18 were detected in 166 women who were followed for a period of 5 years, as previously described (1). White women had 78 (60%) of the 130 infections with European HPVs 16 and 21 (65%) of the 32 infections with European HPV 18. In addition, one white and three nonwhite women were positive for European variants of both HPV types. Prevalent and incident HPVs 16 and 18 infections cleared at comparable rates between white and nonwhite women who were infected with European variants of these two types (P = .436, Fig. 1).

Comparable distributions of clearance times were observed for prevalent and incident infections with HPVs 16 or 18 that were analyzed independently and compared European and non-European variants in the two racial categories described above.

Our results are, however, more in line with those of Hildesheim et al. (4), who did not observe any ethnic difference between individuals with European HPV16 variants in a study conducted in Costa Rica. In that study, microsatellite markers were analyzed to determine the degree of genetic relatedness among individuals. The lack of an association between persistence of a given variant and the racial ancestry of the host in our study and in that of Hildesheim et al. may have originated from the greater racial admixing in the two Latin American populations studied compared with that in the US population. At least for the Brazilian population, it has been shown that the physical appearance of an individual is a poor predictor of genomic African ancestry (5). In the study of Xi et al., the analysis was limited to white and African American women, which are two visibly distinct ethnic groups in the United States.

Xi et al. provided evidence for an evolutionary process that resulted in greater adaptability of certain intratypic variants to specific human population groups. This process likely results from a complex interplay between multiple genetic polymorphisms in HPV and its human host, some of which may mediate mechanisms of susceptibility and immune evasion. Unfortunately, racial admixing in Brazil and in other Latin American countries may not permit ready corroboration of this phenomenon.

**Fig. 1.** Persistence of prevalent and incident infections with European variants of human papillomaviruses 16 and 18 in white and nonwhite women from the Ludwig/McGill cohort. The proportions remaining positive and numbers of women for each racial category are as follows: for white women, 0.35 (95% confidence interval [CI] = 0.25 to 0.44), n = 34 at 12 months; 0.13 (95% CI = 0.07 to 0.20), n = 12 at 24 months; and 0.08 (95% CI = 0.03 to 0.15), n = 7 at 36 months; for nonwhite women, 0.45 (95% CI = 0.32 to 0.56), n = 29 at 12 months; 0.18 (95% CI = 0.09 to 0.28), n = 12 at 24 months; and 0.10 (95% CI = 0.04 to 0.18), n = 7 at 36 months.

**References**


Notes
Affiliations of authors: Department of Virology, Ludwig Institute for Cancer Research, São Paulo, Brazil (LS, SF, LLV); Department of Biochemistry, Chemistry Institute, University of São Paulo, São Paulo, Brazil (LS); Division of Cancer Epidemiology (HT, ELF) and Department of Family Medicine (EDF), McGill University, Montreal, Canada.

Correspondence to: Luisa Lina Villa, PhD, Ludwig Institute for Cancer Research, R Prof Antonio Prudente 109, 4th Fl, 01509-010 São Paulo, SP, Brazil (e-mail: l.lvilla@ludwig.org.br).

DOI: 10.1093/jnci/djk136
© The Author 2007. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

Response
Sichero et al. report an interesting finding and make an important observation. Their study in Brazil showed no difference between whites and nonwhites in clearance rates of European variants of human papillomaviruses (HPV) 16 and 18. In contrast, our United States–based study (1) showed more rapid clearance of European variants of HPV16 and HPV18 among African American women than among white women. It is likely that the observed lack of association between viral variants and time to clearance in the Brazilian study could be attributed in part to more racial admixing in Brazil than in the United States. It is also possible that differences in the specificity of racial categories used in each study contributed to the discrepant findings.

To illustrate how racial classification affects the outcome of interest, we revisited our data by including all three race categories, American Indian, or Alaskan native. The overall likelihood of remaining positive was statistically significantly higher among white women than among African American women; it was intermediate for women classified as Asian, Pacific Islander, American Indian, or Alaskan native. The overall likelihood of remaining positive was statistically significantly higher among white women than among African American women; it was intermediate for women classified as Asian, Pacific Islander, American Indian, or Alaskan native. The overall likelihood of remaining positive was statistically significantly higher among white women than among African American women; it was intermediate for women classified as Asian, Pacific Islander, American Indian, or Alaskan native (Fig. 1).

A similar pattern was observed for women with HPV18 European variants. Grouping women classified as Asian, Pacific Islander, American Indian, or Alaskan native into either the white or African American category would attenuate the race-related risk difference.

The lack of association between genetic relatedness and detection of HPV16 European versus non-European variants in the Costa Rica study (2) is not surprising because the non-European HPV16 variant group in that study included both African and Asian American variants. Asian American variants of HPV16 are relatively common in American Indian women. Moreover, a study of a panel of 10 population-specific alleles found that American Indians and Europeans living in Brazil had a similar ranking on a scale of African ancestry (3). The statistically significant association between HPV16 variants and human leukocyte antigen (HLA) alleles found in the Costa Rica study supports our findings and indicates that specific HLA haplotypes may be associated with inadequate immune presentation of epitopes encoded by particular HPV variants, thereby affecting their capacity to become established or to replicate.

LONG FU XI
LAURA A. KOUTSKY

Fig. 1. Kaplan–Meier estimates of proportion of women remaining positive for viral DNA from the time of enrollment among white women (solid line), African American women (dashed line), and women classified as Asian, Pacific Islander, American Indian, or Alaskan native (other race, dotted line) who were infected with human papillomavirus 16 European variants. Women with high-grade cervical neoplasia at enrollment or during follow-up were censored at the time of initial diagnosis (plus = censor indicator). The P value for the overall likelihood of remaining positive was less than .001 between white and African American women and .21 and .17 for comparing women from other racial groups with white and African American women, respectively. *Number becoming negative, number censored during the interval, and number remaining positive at the beginning of the interval. †Other race was defined as Asian, Pacific Islander, American Indian, or Alaskan native.

References


Notes
The work was supported by Public Health Service grant CA 84396 to L. F. Xi. Dr Koutsky is currently conducting research sponsored by Merck.

The study protocol was approved by the institutional human subject review board of the University of Washington.

The authors have no commercial or other associations that might pose a conflict of interest.

Affiliations of authors: Department of Pathology (LFX), School of Medicine and Department of Epidemiology (LFX, LAK), School of Public Health and Community Medicine, University of Washington, Seattle, WA.

Correspondence to: Long Fu Xi, MD, PhD, 1914 North 34th St, Ste 300, Seattle, WA 98103 (e-mail: longfu@u.washington.edu).

DOI: 10.1093/jnci/djk137
© The Author 2007. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.