

Short Communication

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High Rate of Multiple Concurrent Human Papillomavirus Infections among HIV-Uninfected South African Adolescents

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Abstract

Background: The epidemiology and impact of multiple concurrent Human papillomavirus (HPV) infections on the natural history of cervical disease is uncertain, but could have significant implications for cervical cancer prevention and HPV vaccination strategies.

Methods: A cross-sectional prevalence study was conducted to determine the overall prevalence of HPV and the rate of multiple concurrent HPV infections, in a cohort of sexually active HIV-uninfected South African adolescents. HPV genotyping was performed using the polymerase chain reaction.

Results: Overall prevalence of HPV was 64.1%. Multiple concurrent HPV infections were found in 43.6% of participants and 68% of HPV-infected participants. Non-vaccine high-risk HPV (HR-HPV) genotypes were found much more often than vaccine types (HPV16 and HPV18).

Conclusions: Our cohort of young South African females was found to have a high overall prevalence of HPV and multiple concurrent HPV infections. Most HR-HPV infections found were genotypes other than HPV16 or HPV18.

Keywords

Human papillomavirus; Multiple concurrent infections; Adolescent; South Africa

Introduction

Human papilloma viruses (HPV) cause cervical cancer [1], the single largest cause of years of life lost from cancer in the developing world [2]. While most infections with HPV are transient [3], some infections persist, causing cervical dysplasia, and ultimately invasive cervical cancer. The impact of multiple concurrent infections with two or more different HPV genotypes on the natural history of infection and cervical disease is a matter of controversy. The epidemiology

and impact of multiple concurrent HPV infections has important implications for HPV vaccination and cervical cancer screening.

South African women are among the highest risk groups for developing and dying from invasive cervical cancer [4]. We aimed to determine the overall HPV prevalence and the prevalence of multiple concurrent cervical HPV infections among a cohort of sexually active HIV-uninfected South African adolescent females with normal cervical cytology. The results of our cross-sectional study reveal an extraordinarily high rate of multiple concurrent HPV infections in our study population. We present our results in light of previously reported prevalence rates, and discuss the implications of multiple concurrent HPV infections.

Methods

Between July 2010 and April 2012, we conducted a cross-sectional prevalence study, in which cervical specimens were collected from 39 sexually active HIV-uninfected South African adolescent females who were being screened for possible recruitment into an HPV vaccine acceptability study. None of the study participants had been vaccinated against HPV at the time of enrollment, and all underwent HIV testing to confirm HIV-negative status. HPV DNA analysis was conducted on specimens from all study participants, and HPV Genotyping was performed using Roche's Linear Array[®] Test (Roche Diagnostics, 9115 Hague Road, Indianapolis, Indiana 46250, USA). This detection kit amplifies target DNA utilizing polymerase chain reaction, and is designed to detect 37 human genital HPV genotypes, including all 15 "high-risk" oncogenic HPV types (HR-HPV), as well as the three HPV types identified as "probable high-risk" [5].

Cervical smears were obtained from 30 of the 39 participants, and were reported in accordance with the Bethesda system [6]. Data analysis was conducted using R statistical software. Ethical approval was granted by the review boards of the Universities of Rochester, Cape Town, and the Witwatersrand, and informed consent was obtained from all participants.

Results

The mean age of our cohort was 16.88 years (median 17.27; IQR 1.22). None of the covariates for which we collected data (weight, smoking history, number of sexual partners, pregnancy history and contraception use), were significantly associated with the risk of having multiple concurrent infections (data not shown). Among the 30 participants who had pap smears, all were normal, except one who had atypical squamous cells of undetermined significance.

The prevalence of HPV overall, as well as the proportion of subjects with multiple concurrent HPV infections are presented in table 1. Overall, 25 of 39 (64.1%) participants were infected with at least one HPV type, and 21 (54%) were infected with at least one HR-HPV. Seventeen (43.6%) of the participants had multiple concurrent infections. Among the participants who were HPV positive, 68% were infected with multiple types.

Interestingly, despite the high proportion of subjects infected with HR-HPV, the proportion infected with the vaccine genotypes

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(HPV16, and/or HPV18), was modest at 15.4%. Furthermore, among HR-HPV infected participants, 90.5% were infected with a non-vaccine genotype.

Figure 1 shows the overall prevalence of each genotype found in our cohort, as well as the portion of that prevalence that occurred in the setting of multiple concurrent infections. For example, all four occurrences of HPV16 were found in the presence of at least one other genotype, whereas one of the two occurrences of HPV18 was found as a solitary infection.

Discussion

Sub-Saharan Africa has the highest regional prevalence of HPV infection in the world [7,8]. Although the age-standardized prevalence of HPV in this region is approximately five times higher than that in Europe, most Sub-Saharan populations have limited access to HPV vaccination and secondary cervical cancer preventive services [8]. In a 2007 meta-analysis of worldwide HPV prevalence among cytologically normal women, the prevalence for Africa overall was reported as 22.1% [7]. This is significantly lower than the 64% prevalence found in our cohort. A similar pooled analysis of worldwide HPV prevalence studies found the prevalence of multiple concurrent HPV infections to be 2.6%, compared to a rate of 44% in our cohort.

Past studies of South African populations have identified high prevalence rates of HPV. Allan et al. [9] found an overall HPV prevalence of 20.4%, and an 8.8% prevalence of multiple concurrent infections among women with normal cervical cytology. Said et al. [10] reported a 40% overall HPV prevalence among cytologically normal South African women, and multiple infections in 48% of those who were HPV positive. The results from our cohort, although smaller in size, stand out even among these regional data. While higher than normal rates of multiple concurrent HPV infection would be expected among HIV-infected women [11,12], our study population consisted entirely of HIV-uninfected young women. One factor contributing to this high prevalence may be the young age of our cohort. A number of studies have found that an increased risk of multiple concurrent HPV infections is associated with younger age [13-15]. Although our cohort had an extremely high prevalence of HR-HPV (54%), we found a relatively low prevalence of the vaccine HR-HPV genotypes (HPV16 and HPV18). This raises concerns that even if widely available, the current HPV vaccines may not prevent infection with the majority of HR-HPV in this population.

The significance of multiple concurrent HPV infections is a matter of ongoing debate, and there is no clear consensus in the literature, regarding the impact of this phenomenon on the natural history of cervical cancer. It has been observed for well over a decade

Table 1: Proportion of sample population with HPV infection and multiple concurrent HPV infections (N=39).

	Observed	Proportion	95% CI ^a
Any HPV	25	0.641	(0.4718, 0.788)
Any HR-HPV	21	0.538	(0.3718, 0.6991)
Any LR-HPV	15	0.385	(0.2336, 0.5538)
Multiple concurrent HPV infection (any combination of genotypes)	17	0.436	(0.2781, 0.6038)
Multiple concurrent HPV infection given HPV positive	17	0.68	(0.465, 0.8505)
Positive for vaccine HR-HPV (HPV 16 and/or HPV 18)	6	0.154	(0.0586, 0.3053)
Positive for non-vaccine HR-HPV	19	0.487	(0.3242, 0.6522)
Positive for non-vaccine HR-HPV given positive for any HR-HPV	19	0.905	(0.6962, 0.9883)

^aThe methods used are exact binomial 95% confidence intervals for proportions based on the Clopper-Pearson method

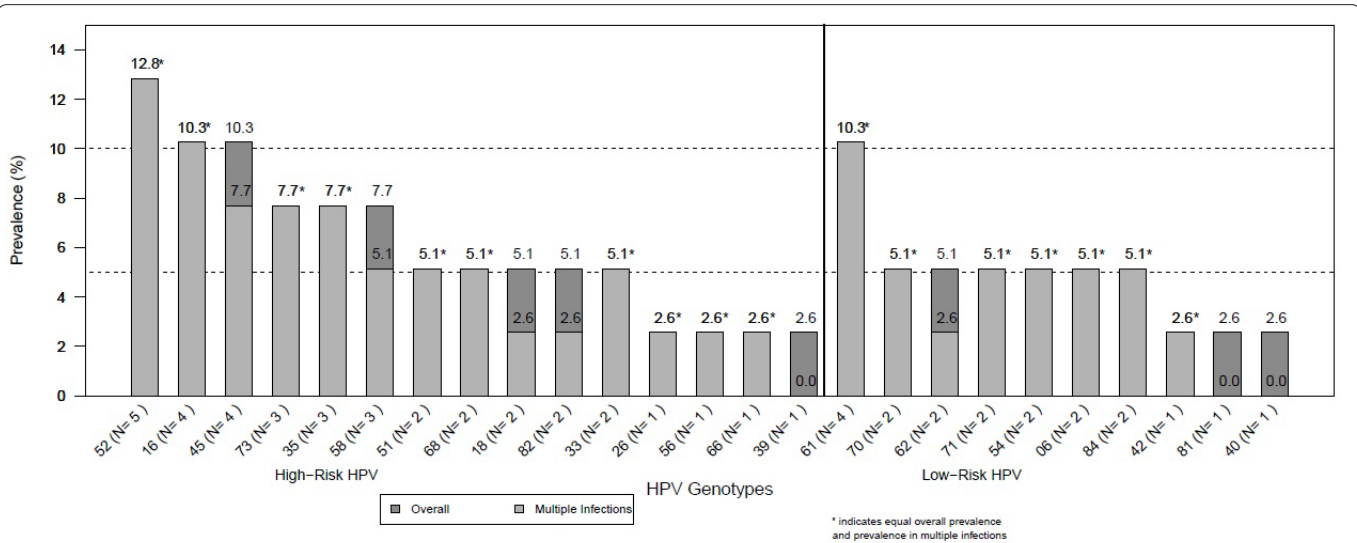


Figure 1: Overall prevalence of individual HPV genotypes and portion of prevalence that occurs in the setting of multiple concurrent infections.

that an increased duration of infection with HR-HPV is associated with an increased risk of cervical dysplasia [16,17]. There is some evidence that multiple concurrent HPV infections are associated with increased duration of infection, and, therefore could increase the risk of cervical disease, compared to single HPV infections. Trottier et al. [18] found that the mean duration of infection for any HPV infection increased from 10.2 months to 12.7 months, when at least one HPV co-infection was present. The mean duration of an HR-HPV infection increased from 10.1 to 13.5 months, and the mean duration of an HPV16 infection increased from 11.0 to 15.4 months [18]. Other studies have not identified any increase in duration of infection with multiple concurrent infections [19,20].

A number of studies have investigated whether there may be an increased risk of cervical disease associated with multiple concurrent HPV infections. Bello et al. [21] identified a linear relationship between the number of concurrent infections and the class of risk for both cytological and histological findings. Other studies have identified a similar increased risk [22-25]. While Chaturvedi et al. [23] found this increased risk of multiple concurrent infections to be additive in nature, Trottier et al. [22] concluded that multiple infections act synergistically in carcinogenesis. In contrast, in a analysis of cytology samples from a screening population, Cuschieri et al. [13] found that there was no association between the number of HPV infections and the severity of cervical dysplasia.

Finally, there is ongoing uncertainty, as to whether different HPV genotypes interact biologically to cluster in co-infection. Clustering could have significant implications for the impact of HPV vaccination, as it relates to cross protection. To date, the results of research into clustering of HPV genotypes in co-infection has been mixed. While some investigators have reported positive evidence for this phenomenon [26,27], many have not [28-31].

Understanding the epidemiology of multiple concurrent HPV infections and their impact on the natural history of cervical disease is essential to planning effective cervical cancer screening and HPV vaccination strategies. Our study, while limited by a small sample size, describes an unusually young and high-risk population, with an extraordinarily high overall HPV prevalence and prevalence of multiple concurrent HPV infections.

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References

- Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV (2002) The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 55: 244-265.
- Yang BH, Bray FI, Parkin DM, Sellors JW, Zhang ZF (2004) Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. *Int J Cancer* 109: 418-424.
- Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, et al. (2010) Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst* 102: 315-324.
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, et al. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 127: 2893-2917.
- Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, et al. (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 348: 518-527.
- Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, et al. (2002) The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 287: 2114-2119.
- de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, et al. (2007) Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis* 7: 453-459.
- Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJ, et al. (2005) Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet* 366: 991-998.
- Allan B, Marais DJ, Hoffman M, Shapiro S, Williamson AL (2008) Cervical human papillomavirus (HPV) infection in South African women: implications for HPV screening and vaccine strategies. *J Clin Microbiol* 46: 740-742.
- Said HM, Ahmed K, Burnett R, Allan BR, Williamson AL, et al. (2009) HPV genotypes in women with squamous intraepithelial lesions and normal cervixes participating in a community-based microbicide study in Pretoria, South Africa. *J Clin Virol* 44: 318-321.
- Clifford GM, Goncalves MA, Franceschi S (2006) Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS* 20: 2337-2344.
- Levi JE, Fernandes S, Tateno AF, Motta E, Lima LP, et al. (2004) Presence of multiple human papillomavirus types in cervical samples from HIV-infected women. *Gynecol Oncol* 92: 225-231.
- Cuschieri KS, Cubie HA, Whitley MW, Seagar AL, Arends MJ, et al. (2004) Multiple high risk HPV infections are common in cervical neoplasia and young women in a cervical screening population. *J Clin Pathol* 57: 68-72.
- Rousseau MC, Abrahamowicz M, Villa LL, Costa MC, Rohan TE, et al. (2003) Predictors of cervical coinfection with multiple human papillomavirus types. *Cancer Epidemiol Biomarkers Prev* 12: 1029-1037.
- Mejlhede N, Bonde J, Fomsgaard A (2009) High frequency of multiple HPV types in cervical specimens from Danish women. *APMIS* 117: 108-114.
- Schlecht NF, Kulaga S, Robitaille J, Ferreira S, Santos M, et al. (2001) Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA* 286: 3106-3114.
- Ho GY, Burk RD, Klein S, Kadish AS, Chang CJ, et al. (1995) Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst* 87: 1365-1371.
- Trottier H, Mahmud S, Prado JC, Sobrinho JS, Costa MC, et al. (2008) Type-specific duration of human papillomavirus infection: implications for human papillomavirus screening and vaccination. *J Infect Dis* 197: 1436-1447.
- Campos NG, Rodriguez AC, Castle PE, Herrero R, Hildesheim A, et al. (2011) Persistence of concurrent infections with multiple human papillomavirus types: a population-based cohort study. *J Infect Dis* 203: 823-827.
- Rousseau MC, Pereira JS, Prado JC, Villa LL, Rohan TE, et al. (2001) Cervical coinfection with human papillomavirus (HPV) types as a predictor of acquisition and persistence of HPV infection. *J Infect Dis* 184: 1508-1517.
- Bello BD, Spinillo A, Alberizzi P, Cesari S, Gardella B, et al. (2009) Cervical infections by multiple human papillomavirus (HPV) genotypes: Prevalence and impact on the risk of precancerous epithelial lesions. *J Med Virol* 81: 703-712.
- Trottier H, Mahmud S, Costa MC, Sobrinho JP, Duarte-Franco E, et al. (2006) Human papillomavirus infections with multiple types and risk of cervical neoplasia. *Cancer Epidemiol Biomarkers Prev* 15: 1274-1280.
- Chaturvedi AK, Katki HA, Hildesheim A, Rodriguez AC, Quint W, et al. (2011) Human papillomavirus infection with multiple types: pattern of coinfection and risk of cervical disease. *J Infect Dis* 203: 910-920.
- Sasagawa T, Basha W, Yamazaki H, Inoue M (2001) High-risk and multiple human papillomavirus infections associated with cervical abnormalities in Japanese women. *Cancer Epidemiol Biomarkers Prev* 10: 45-52.
- van der Graaf Y, Molijn A, Doornwaard H, Quint W, van Doorn LJ, et al. (2002) Human papillomavirus and the long-term risk of cervical neoplasia. *Am J Epidemiol* 156: 158-164.

26. Vaccarella S, Franceschi S, Snijders PJ, Herrero R, Meijer CJ, et al. (2010) Concurrent infection with multiple human papillomavirus types: pooled analysis of the IARC HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev* 19: 503-510.
27. Mejlhede N, Pedersen BV, Frisch M, Fomsgaard A (2010) Multiple human papilloma virus types in cervical infections: competition or synergy? *APMIS* 118: 346-352.
28. Thomas KK, Hughes JP, Kuypers JM, Kiviat NB, Lee SK, et al. (2000) Concurrent and sequential acquisition of different genital human papillomavirus types. *J Infect Dis* 182: 1097-1102.
29. Fife KH, Cramer HM, Schroeder JM, Brown DR (2001) Detection of multiple human papillomavirus types in the lower genital tract correlates with cervical dysplasia. *J Med Virol* 64: 550-559.
30. Chaturvedi AK, Myers L, Hammons AF, Clark RA, Dunlap K, et al. (2005) Prevalence and clustering patterns of human papillomavirus genotypes in multiple infections. *Cancer Epidemiol Biomarkers Prev* 14: 2439-2445.
31. Vaccarella S, Franceschi S, Herrero R, Schiffman M, Rodriguez AC, et al. (2011) Clustering of multiple human papillomavirus infections in women from a population-based study in Guanacaste, Costa Rica. *J Infect Dis* 204: 385-390.

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