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High-risk human papillomavirus among HIV-infected women with normal cervical cytology: a pilot study in Jos, Nigeria

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Abstract
Background Cervical cancer is strongly linked to high-risk human papillomavirus (HR-HPV) and is typically preceded by cytological abnormalities. Less is known in patients with normal cervical cytology (NCC). We investigated the epidemiology of HR-HPV among HIV-infected women with NCC.
Methodology We conducted a cross-sectional study between January and June 2011 among HIV-infected women with NCC at an adult HIV clinic in Jos, Nigeria. Cervical sampling and analysis for HR-HPV by hybrid capture (HC2) with signal amplification was done to determine presence of one or more of the following HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 or 68. Epidemiologic factors associated with HR-HPV were determined using bivariate statistics and multivariate logistic regression.
Results We evaluated 103 HIV-infected women with Pap cytology. The median age of the women was 32 years (range 21–49). Ninety-seven (94.2 %) had NCC. Cervical samples for HR-HPV DNA testing were available from 89/97 (91.8 %) of the HIV-infected women with NCC. Of the 89 women with cervical samples for HR-HPV DNA testing, 40 (44.9 %) had detectable HR-HPV by HC2 giving a HR-HPV prevalence of 44.9 % (95 % CI 33.9–55.5 %). Age < 30 years was associated with HR-HPV (OR 2.69 [95 % CI 1.05–6.91, $p = 0.039$]) while history of previous abortion showed an inverse association with HR-HPV (OR 0.33[95 % CI 0.15–0.94, $p = 0.039$]).
Conclusion The prevalence of HR-HPV is seemingly high among HIV-infected women with NCC in our clinical setting. These data provide support for further investigation of the clinical implications of positive HR-HPV among HIV-infected women with NCC report in cervical cancer prevention programs in Nigeria.

Keywords Human papillomavirus · HIV · Normal cervical cytology · Nigeria

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Introduction

Cervical cancer is the second most common malignancy among women worldwide [1], with approximately 454,000 new cases and 200,000 attributable deaths in 2010 [2]. Developed countries with comprehensive screening programs have recorded a sustained decline in cervical cancer incidence and mortality; however, many developing countries are experiencing an upsurge [2, 3]. In Nigeria, 11,431 cases were reported in 2010 compared to 5,714 in 1980 [2] while 5,952 deaths were attributed to cervical cancer in 2010 compared to 3,158 in 1980 [2]. Cervical cancer is largely preventable when cytological precursors and early pre-invasive stages are diagnosed and effectively

treated. Cytological examination of cervical cells obtained through Papanicolaou (Pap) smear continues to be an effective cervical cancer screening modality, but in resource-limited settings it has been shown to have high false-negative and false-positive rates [4, 5]. Therefore, better modalities or technologies for cervical cancer screening are greatly needed to make an impact on this disease worldwide.

Human papillomavirus (HPV) types 16 and 18 cause approximately 70 % of cervical cancer cases [6–8], and the eight most common HPV genotypes (16, 18, 31, 33, 35, 45, 52 and 58) account for 90 % of cases [9, 10]. The oncogenic effect of high-risk HPV (HR-HPV) types is related to their ability to persist in cervical tissues. Cellular immune responses play a key role in HPV clearance, hence HIV-induced immune suppression promotes HPV persistence and carcinogenesis [11–14]. Routine HR-HPV testing is being incorporated into cervical cancer screening in developed countries because of improved sensitivity and predictive value.

The role of HR-HPV screening in developing countries is unclear, although a randomized trial in India showed superiority of HPV testing in preventing advanced cervical cancer incidence and death compared to conventional cytology [15]. Since HPV types in cervical cancer sometimes match the types present at earlier time-points with normal cytology [16], and HIV infection predisposes to HPV persistence, we hypothesized that opportunities for cervical cancer prevention are missed in HIV-infected women with NCC and unrecognized HR-HPV. To investigate the potential scope of this problem in a developing country, we determined the prevalence and epidemiologic factors associated with HR-HPV in a cohort of HIV-infected women with normal cytology in Jos, Nigeria.

Methodology

Study setting

This study was conducted at the Reproductive Health Unit (RHU) of the APIN/Harvard PEPFAR HIV Clinic, Jos University Teaching Hospital (JUTH), Nigeria. The RHU was set up in 2008 and is staffed by two reproductive health nurses and a gynecologist to address issues related to contraception and offer Pap smear for cervical cancer screening.

Routine care at JUTH includes CD4+ T cell (Partec, Germany) and viral load (Roche Amplicor 1.5, lower detection limit 400 copies/ml) measurement before antiretroviral therapy (ART), then approximately every 3 months during ART. Initiation of ART follows the Nigerian National Guidelines for HIV and AIDS treatment and care in adolescents and adults, 2010 [17]. Other information routinely collected in the clinical care of patients at JUTH included the following: demographics, ART history and co-infections (hepatitis B, hepatitis C and tuberculosis). At enrollment, each patient gave written informed consent for collection and use of their medical information for research purposes. In addition, for the current study, each participant provided separate informed consent to obtain a cervical specimen for research purposes. Human Subjects Research Ethics Committee of JUTH provided ethical approval and a secondary use of data approval was granted by the Harvard School of Public Health to use CD4+ T cell count, viral load and other relevant patient data.

Study design, population and procedures

Between January and June 2011, we recruited participants from HIV-infected women who presented to the RHU for Pap smear as part of routine reproductive health care for all HIV-infected women. Inclusion criteria were: (1) confirmed HIV diagnosis by Western blot; (2) age $\geq$18 years; and (3) signed informed consent to the study. Pregnant women and those with previous treatment for cervical premalignant lesions, hysterectomy or invasive cervical malignancy were excluded. Being a pilot study, we set out to enrolled the first consecutive 100 participants who had normal cervical cytology (NCC) to collect cervical specimens for subsequent HR-HPV DNA testing.

A detailed questionnaire was administered to each participant to determine age, age at first coitus, parity, duration of HIV infection, ART history, previous abortions, history of contraception, previous Pap smear, smoking, and alcohol consumption. Patient information not recalled by study participants such as duration of HIV disease, ART history, etc., were extracted from their electronic database. The RHU gynecologist performed pelvic examination that included visual inspection of the cervix followed by ectocervical and endocervical sampling using a cytobrush. The endocervical and ectocervical samples were smeared on two pre-labeled slides, immediately fixed in an alcohol-containing jar, and later stained according to the Pap technique. Two cytopathologists independently examined and interpreted each slide. Only those with concordant normal cytology results were included in this study. Cytological findings were reported according to the 2001 Bethesda system [18].

Participants with normal cytology returned within five working days for another sampling using an approved Digene HPV cervical sample collection device and storage medium (Digene Corporation, Gaithersburg, USA). Samples for HPV testing were stored at −80 °C and batch shipped (CDC shipment permit was obtained for this

purpose) to Quest Laboratories, Chicago, USA, for analysis. The samples were analyzed for HR-HPV by hybrid capture two (HC2) with signal amplification according to the manufacturer's specifications. Positivity for HR-HPV signified presence of one or more of the following HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.

Data collection and statistical analysis

We created a study database that included socio-demographic parameters, CD4+ T cell count, viral load, and ART history as well as results of the questionnaire, cytology and HC2 HR-HPV testing. All analyses were performed using STATA version 11.0, College station, TX, USA.

We generated summary statistics to compare baseline socio-demographic characteristics of study participants. To determine the factors associated with HR-HPV positivity, we created binary indicator variables for age, current CD4+ T cell count, current viral load, ART status, previous abortion, contraceptive history, alcohol, and smoking history. We performed bivariate comparisons of these factors between patients with and without HR-HPV using Pearson's Chi-square test or Fisher's exact test where applicable for categorical variables and student's *t* test for continuous variables. We examined risk factors in adjusted analyses using multivariate logistic regression with model variables based on bivariate statistical comparisons and clinical importance. Statistical significance was based on 95 % confidence and *p* value <0.05. Model fitness was assessed using the Hosmer–Lemeshow goodness-of-fit test (a *p* value of >0.05 suggest good model fit [19]).

Results

Study population

A total of 119 HIV-infected women presented at the RHU for Pap cytology evaluation (16 were excluded from having Pap smears because of menstruation, abnormal bleeding, or technical difficulties visualizing the cervix). Thus, 103 women underwent Pap smears and were administered the questionnaire. Of these, 97 (94.2 %) had NCC while 6 (5.8 %) had abnormal cytology: 3 (2.9 %) with atypical squamous cells of undetermined significance (ASCUS), 2 (1.9 %) with low-grade squamous intraepithelial lesions (LSIL), and 1 (0.97 %) case of high-grade squamous intraepithelial lesions (HSIL). Eighty-nine (91.8 %) of the women with normal cytology completed testing for HR-HPV DNA, and constituted the final study population (Table 1).

Table 1 Socio-demographic characteristics of HIV-infected women with normal cytology associated with HR-HPV ($N = 89$)

Variable	Positive HR-HPV $N = 40$	Negative HR-HPV $N = 49$	*p* value
Age (years)	31.68 ± 4.8	32.80 ± 4.3	0.253*
Age at first coitus (years)	18.5 ± 3.0	19.0 ± 3.1	0.396*
Marital status ($N = 88$)			
Never married	6 (85.7)	1 (14.3)	0.198‡
Married	28 (42.4)	38 (57.6)	
Separated/divorced	3 (37.5)	5 (62.5)	
Widowed	2 (28.6)	5 (71.4)	
Level of education ($N = 88$)			
≤Primary	8 (38.1)	13 (61.9)	0.663‡
Secondary	18 (45.0)	22 (55.0)	
Tertiary	13 (48.1)	14 (51.9)	
Smoking history ($N = 88$)			
Never	37 (45.1)	45 (54.9)	0.689‡
Past/current	2 (33.3)	4 (66.7)	
Alcohol history ($N = 88$)			
Never	30 (51.7)	28 (48.3)	0.127‡
Past/current	9 (30.0)	21 (70.0)	
Parity ($N = 88$)			
0	6 (50.0)	6 (50.0)	0.174‡
≥1	33 (43.4)	43 (56.6)	
History of abortion ($N = 85$)			
Yes	16 (33.3)	32 (66.7)	0.016‡
No	22 (59.5)	15 (40.5)	
Contraceptive history ($N = 89$)			
Never	11 (47.8)	12 (52.2)	0.938†
Past	12 (42.9)	16 (57.1)	
Current	17 (44.7)	21 (55.3)	

Some variables did not add to 89 due to missing information. All data presented are *N* (%) unless otherwise specified

* Student *t* test, ‡ Fisher's Exact, † Pearson's Chi-square

Table 2 Logistic regression of factors associated with HR-HPV among women with normal cytology infected with HIV in Jos, Nigeria ($N = 85$)

Variable	OR (unadjusted)	95 % CI, (*p* value)	OR (Adjusted)	95 % CI, (*p* value)
Age < 30 years	2.5	1.04–6.01, (0.040)	2.70	1.05–6.92, (0.039)
CD4+ <500 cells/mm^3	1.38	0.58–3.28, (0.470)	0.70	0.26–1.88, (0.478)
Viral load < 400 copies/ml	0.83	0.32–2.14, (0.710)	0.77	0.25–2.35, (0.647)
Previous abortion (yes/no)	0.34	0.14–0.82, (0.018)	0.33	0.15–0.94, (0.039)

OR unadjusted odds ratio, *AOR* adjusted odds ratio, *CI* confidence interval

The study population had a median age of 32 years (range 21–49), and the majority were non-smokers (93.0 %), non-users of alcohol (65.9 %), married (75.3 %), multiparous (74.1 %), and had a history of abortion (56.5 %). Current contraceptive users were 43.5 and 45.9 % had a secondary level education. 95 % were on ART and 73.2 % had undetectable viral load. Median CD4+ T cell count was 578 cells/mm^3 (133–1,153) and median viral load was <400 RNA copies/ml (400–77,442).

Prevalence of HR-HPV among women with normal cytology and associated factors

Forty women had HR-HPV giving a point prevalence of 44.9 % (95 % CI 33.9–55.5 %). Bivariate analyses showed age <30 years was significantly associated with a higher likelihood of having HR-HPV (OR 2.5 95 % CI 1.0–6.0; $p = 0.04$). Women who reported previous abortion had significantly lower likelihood of HR-HPV detection (16/48, 33.3 %) compared with women with no previous abortion (22/37, 59.5 %) (OR 0.34, 95 % CI 0.14–0.83, $p = 0.018$). Marital status, education, parity, smoking, alcohol use, and contraceptive use were not significantly associated with HR-HPV detection (all $p > 0.05$). There was no significant difference in the likelihood of having HR-HPV between women with undetectable viral load and those with detectable levels (OR = 0.83, 95 % CI 0.32–2.15, p value 0.706). The median CD4+ T cell count of the women was 578 cells/mm^3 (range 133–1,153). There was no significant difference in median CD4+ T cell counts between women with HR-HPV compared with women negative for HR-HPV ($p = 0.585$; non-parametric sample-equality-of-median test).

In a multivariate logistic regression model including age category <30 years, previous abortion (yes or no), CD4+ T cell count (dichotomized at 500 cell/mm^3) and viral load (dichotomized at 400 copies/ml), age <30 years, and no previous abortion were independently associated with higher likelihood of HR-HPV detection (OR 2.69 [95 % CI 1.05–6.91, $p = 0.039$] and 2.64 [95 % CI 1.05–6.64, $p = 0.039$]), respectively (Table 2). The model fit was good (Hosmer–Lemeshow goodness-of-fit p value 0.743) [19].

Discussion

In this study, we found a high prevalence (44.9 %) of HR-HPV among HIV-infected women with NCC. This is the first report of prevalence of HR-HPV among HIV-infected women with NCC from Nigeria to our knowledge. In Uganda, 38 % of women with normal Pap smears had a positive HPV cervical assay with an overall HPV infection of 59.5 % among HIV-infected women [20]. The authors noted that the presence of HR-HPV was significantly associated with abnormal findings on Pap smear. Among HIV-infected Rwandan women, HR-HPV was found in 33 % of women with normal Pap cytology [21]. The relative variation in the prevalence of HR-HPV among HIV-infected women with normal cytology in these settings could be attributed to differences in demographic and immunologic characteristics of the studied population and the methods for the detection of HR-HPV. In the Ugandan and Rwandan studies, specific HR-HPV genotypes were detected using PCR assay, while HC2, which detects any of the 13 HR-HPV types was the method of detection among our study population.

We also investigated factors associated with HR-HPV in this setting. We found age less than 30 years to be associated with increased likelihood of HR-HPV. Previous studies [20–22] have similarly reported a younger age (<30 years) to be significantly associated with presence of HR-HPV although these studies did not focus on HIV-infected women with normal cytology as in our study population. It has been documented that even though women usually acquire HPV early after sexual activity debut, the majority clear the infection through cellular mediated immunity within 12–24 months [23, 24]. In light of anecdotal evidence of a rising number of invasive cervical cancers among young HIV-infected women less than 30 years in our hospital population, our data increases the urgency for further studies and targeted intervention in this population.

One surprising, but interesting finding in our study is that women who reported previous abortion had a 66 % lower risk of HR-HPV. Recent reports have also shown an inverse association between intrauterine device use and development of invasive cervical cancers [25]. A postulated central mechanism is that cervical trauma and inflammation induced by gynecologic procedures or foreign objects may increase HR-HPV clearance and thus, reduce viral oncogenic potential in the cervical tissues. More studies are required to confirm this and probe the potential impact on subsequent risk of SIL and cervical cancer. Other socio-demographic variables (marital status, parity, contraceptive use, educational level, smoking, and alcohol consumption) were not significantly associated with presence of HR-HPV among our study population. A previous study [26] also showed that socio-demographic factors were not associated with oncogenic HPV among women with low-grade cytologic abnormalities [<cervical intraepithelial neoplasia (CIN) 2], but an association with high-grade cervical lesions (≥CIN 3) was found.

We did not detect an association between HR-HPV positivity and viral load or current CD4+ T cell count. Of note, about 95 % of the study participants were on ART

(mean duration of 47 months, 73 % undetectable viral load). Median CD4+ T cell count was 578 cells/mm^3 and median viral load was <400 RNA copies/ml. While our findings may be related to the relative immune competence of our study population, the incidence of HPV-related cervical disease has not changed substantially in the era of ART [27]. Also, ART did not alter the prevalence or incidence of HPV infection in HIV-infected adolescents during short-term follow-up [28].

Notable limitations of our study included the relatively small size of the study population and lack of a comparator group of HIV negative women with NCC. We also did not have data to compare the relative prevalence of HR-HPV among women with abnormal NCC. However, since women with abnormal cytology are usually referred for further management, we deliberately focused on HIV-infected women with NCC. These women are often reassured by health care providers and may never return for follow up examination, likely reducing opportunities for early cancer detection. Cervical samples for cytology and HPV DNA testing were not obtained at the same time, but it is unlikely that the intervening period was long enough to alter our results.

In conclusion, we found HR-HPV in nearly half of HIV-infected women with NCC, most of them were on successful ART. Our next step is to determine whether Pap smear missed precancerous lesions in these women. We postulate this considering a recent study in HIV-uninfected women with normal cytology reported a 15 % prevalence of SIL among those with HR-HPV [29]. We will also perform longitudinal studies to evaluate whether detection of HR-HPV in HIV-infected women despite normal cytology predicts development of cervical dysplasia and/or cervical cancer over time.

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Conflict of interest The authors declare no conflict of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, Naghavi M (2011) Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. Lancet 378(9801):1461–1484
3. Milliez J (2008) Cervical cancer prevention and the millenium development goals. Bull World Health Organ 86:6
4. Deblinta Datta S, Koutsky LA, Ratelle S, Unger ER, Shlay J, McClain T, Weaver B, Kerndt P, Zenilman J, Hagensee M, Suhr CJ, Weinstock H (2008) Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003–2005. Ann Intern Med 148(7):493–500
5. Sawaya GF (2008) Adding human papillomavirus testing to cytology for primary cervical cancer screening: shooting first and asking questions later editorial. Ann Intern Med 148(7):557–559
6. Franco EL, Rohan TE, Villa LL (1999) Epidemiologic evidence and human papillomavirus infection as a necessary cause of cervical cancer. J Natl Cancer Inst 91(6):506–511
7. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NWJ, Heideman DAM, Kenter GG, Cuzick J, Snijders PJF, Meijer CJLM (2012) Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 13(1):78–88
8. Munoz N, Castellasague X, de Gonzalez AB, Gissmann L (2006) HPV in the etiology of human cancer. Vaccine 24:S1–S10
9. Munoz N, Bosch FX, Castellsague X, Diaz M, De Sanjose S, Hammouda D et al (2004) International perspective. Int J Cancer 111:278–285
10. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R et al (2007) Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer 121:621–632
11. Palefsky JM, Holly EA (2003) Immunosuppression and co-infection with HIV. J Natl Cancer Inst Monogr 31:41–46
12. Minkoff H, Feldman J, DeHovitz J, Landesman S, Burk R (1998) A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. Am J Obstet Gynecol 178: 982–986
13. Moscicki AB, Ellenberg JH, Farhat S, Xu J (2004) Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. J Infect Dis 190:37–45
14. Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A et al (2001) Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus-positive and negative women. J Infect Dis 184:682–690
15. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA (2009) HPV screening for cervical cancer in rural India. N Engl J Med 360(14):1385–1394
16. Walboomers JMM, de Roda Husman AM, Snijders PJF, Stel HV, Risse EKJ, Helmerhost TJM, Voorhorst FJ, Meijer CJLM (1995) Human papillomavirus in false negative archival cervical smears: implications for screening for cervical cancer. J Clin Pathol 48:728–732
17. (2010) Antiretroviral therapy in adults and adolescents. In: National guidelines for HIV and AIDS treatment and care in adolescents and adults. Section 3, Federal Ministry of Health, Abuja-Nigeria, pp 10–29
18. Solomon D, Davey D, Kurman R et al (2002) The 2001 bethesda system: terminology for reporting results of cervical cytology. JAMA 287:2114–2119
19. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S (1997) A comparison of goodness-of-fit tests for the logistic regression model. Stat Med 16:965–980
20. Blossom DB, Beigi RH, Farrell JJ, Mackay W, Qadadri B, Brown DR, Rwambuya S, Walker CJ, Kambugu FS, Abdul-Karim FW, Whalen CC, Salata RA (2007) Human papillomavirus genotypes

associated with cervical cytologic abnormalities and HIV infection in Ugandan women. J Med Virol 79(6):758–765
21. Singh DK, Anastos K, Hoover DR, Burk RD, Shi Q, Ngendahayo L, Mutimura E, Cajigas A, Bigirimani V, Cai X, Rwamwejo J, Vuolo M, Cohen M, Castle PE (2009) Human papillomavirus infection and cervical cytology in HIV-infected and HIV-uninfected Rwandan women. J Infect Dis 199(12):1851–1861
22. Musa J, Taiwo B, Goldsmith S, Sutton S, Berzins B, Murphy RL (2011) Predictors of atypical squamous cells of undetermined significance cervical cytology with high-risk human papillomavirus genotypes. Arch Gynecol Obstet 283:343–348
23. Mosciki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N, Darragh TM, Brescia R, Kanowitz S, Miller SB et al (1998) The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. J Pediatr 132:277–284
24. Rodriguez AC, Schiffman M, Herrero R, Wacholder S, Hildesheim A, Castle PE, Solomon D, Burk R (2008) Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst 100:513–517
25. Castellsagué X, Díaz M, Vaccarella S, de Sanjosé S, Muñoz N, Herrero R, Franceschi S, Meijer CJLM, Bosch FX (2011) Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. Lancet Oncol 12:1023–1031
26. Khan MJ, Partridge EE, Wang SS, Schiffman M (2005) Socioeconomic status and the risk of cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mild abnormal cytology. Cancer 104:61–70
27. Adler DH (2010) The impact of HAART on HPV-related cervical disease. Curr HIV Res 8:493–497
28. Shrestha S, Sudenga SL, Smith JS, Bachmann LH, Wilson CM, Kempf MC (2010) The impact of highly active antiretroviral therapy on the prevalence and incidence of cervical human papillomavirus infections in HIV-positive adolescents. BMC Infect Dis 10:295
29. Arora R, Kumar A, Prusty BK, Kailash U, Batra S, Das BC (2005) Prevalence of high-risk human papillomavirus (HR-HPV) types 16 and 18 in healthy women with cytologically negative pap smear. Eur J Obstet Gynecol Reprod Biol 121(1):104–109