NIH Public Access
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Gynecol Oncol. Author manuscript; available in PMC 2009 September 22.

Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia

Groesbeck P. Parham[a,b,*], **Vikrant V. Sahasrabuddhe**[c], **Mulindi H. Mwanahamuntu**[d], **Bryan E. Shepherd**[c], **Michael L. Hicks**[e], **Elizabeth M. Stringer**[a,b], and **Sten H. Vermund**[b,c]

[a]School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

[b]Center for Infectious Disease Research in Zambia, Lusaka, Zambia, USA

[c]School of Medicine, Vanderbilt University, Nashville, TN, USA

[d]University Teaching Hospital, Lusaka, Zambia, USA

[e]Pontiac Cancer Institute, Pontiac, Michigan, USA

Abstract

Objectives—HIV-infected women living in resource-constrained nations like Zambia are now accessing antiretroviral therapy and thus may live long enough for HPV-induced cervical cancer to manifest and progress. We evaluated the prevalence and predictors of cervical squamous intraepithelial lesions (SIL) among HIV-infected women in Zambia.

Methods—We screened 150 consecutive, non-pregnant HIV-infected women accessing HIV/AIDS care services in Lusaka, Zambia. We collected cervical specimens for cytological analysis by liquid-based monolayer cytology (ThinPrep Pap Test®) and HPV typing using the Roche Linear Array® PCR assay.

Results—The median age of study participants was 36 years (range 23-49 years) and their median CD4+ count was 165/μL (range 7-942). The prevalence of SIL on cytology was 76% (114/150), of which 23.3% (35/150) women had low-grade SIL, 32.6% (49/150) had high-grade SIL, and 20% (30/150) had lesions suspicious for squamous cell carcinoma (SCC). High-risk HPV types were present in 85.3% (128/150) women. On univariate analyses, age of the participant, CD4+ cell count, and presence of any high-risk HPV type were significantly associated with the presence of severely abnormal cytological lesions (i.e., high-grade SIL and lesions suspicious for SCC). Multivariable logistic regression modeling suggested the presence of any high-risk HPV type as an independent predictor of severely abnormal cytology (adjusted OR: 12.4, 95% CI 2.62-58.1, *p*=0.02).

Conclusions—The high prevalence of abnormal squamous cytology in our study is one of the highest reported in any population worldwide. Screening of HIV-infected women in resource-constrained settings like Zambia should be implemented to prevent development of HPV-induced SCC.

Keywords

HIV; Cervical Cancer; Screening; Cytology; Zambia

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*Corresponding author. Department of Medicine, Div. of Infectious Diseases-Center for AIDS Research, Center for Infectious Disease Research in Zambia, University of Alabama at Birmingham, Community Care Building, 908-20th Street South, Birmingham, AL, 35294, USA. Fax: +1 205 975 6448. *E-mail address:* gparham@uabmc.edu (G.P. Parham).

Introduction

Each year, across the world, approximately 490,000 women are newly diagnosed and 274,000 women die from invasive cancer of the uterine cervix induced by oncogenic types of human papillomavirus (HPV) [1-3]. The overwhelming majority of women affected by this completely preventable disease live in resource-constrained nations where access to screening services is limited or non-existent [2-5]. In these same settings, during the past decade, the HIV/AIDS pandemic has overwhelmed the health care systems and had an enormous impact on women, particularly those of reproductive age [6]. Of the nations in sub-Saharan Africa, Zambia has one of the highest background prevalence rates of HIV (seroprevalence rate between 16% and 25%) as well as the second highest prevalence rate of invasive cervical cancer in the world (prevalence of 61.1/100,000) [1,7]. Until recently, women living with HIV/AIDS in settings like Zambia had very limited access to antiretroviral therapy and consequently had a very limited survival period after being diagnosed with HIV. However, increasing numbers of women are being linked to antiretroviral therapy treatment programs that have the potential to improve their lifespan long enough for cervical cancer precursors to manifest and progress to invasive cancer [8,9]. As such, HIV-infected women in resource-constrained environments are now at heightened risk for the development and progression of HPV-induced cervical cancer precursors to invasive cancer [10-13]. Thus, it is becoming increasingly necessary to provide regular cervical cancer screening services for these women and to link screening and treatment in such a manner that it ensures compliance.

Unfortunately, there are no clear and appropriate guidelines for screening HIV-infected women who live in resource-constrained nations like Zambia, partly because of the lack of data documenting the background prevalence of these lesions and the accuracy of screening tests and protocols for these high-risk women.

With a goal to develop and evaluate the appropriateness of cervical cancer screening protocols for HIV-infected women living in resource-constrained nations like Zambia, a pilot feasibility study was undertaken among HIV-infected women attending the University of Zambia Teaching Hospital, a tertiary referral center in Lusaka, Zambia. This paper reports the results of the prevalence of cervical cytological abnormalities in these women and its relation to their immunosuppressive state.

Methods

Study setting and participants

This study was approved by the Research Ethics Committee of the University of Zambia and the Institutional Review Board of the University of Alabama at Birmingham. We offered recruitment to 150 consecutive HIV-infected women attending the HIV-care clinic at the University Teaching Hospital in Lusaka. After explanation of the study and clinical procedures, all 150 women provided written informed consent administered in English, Bemba, or Nyanja. Eligibility criteria included prior documented evidence of HIV infection (prior test records of two positive rapid HIV 1/2 tests: Determine® and Capillus®), good mental and physical condition, and current absence of acute illness. We excluded women who were pregnant [menstrual history], had a history of previous diagnosis or treatment of cervical neoplasia, or had undergone hysterectomy. After a clinical and pelvic examination, women showing signs of sexually transmitted infections (e.g., cervicovaginal discharge) were counseled and treated using World Health Organization guidelines for syndromic management and asked to return to the clinic after 2 weeks for study screening and enrollment [14].

Clinical tests

In the clinical protocol, after administering the consent and confirming the eligibility, basic sociodemographic data were collected using a structured questionnaire. A blood sample was collected if no CD4+ cell count was documented in the previous three weeks. A trained gynecologist conducted a physical and pelvic examination in all women. A trained nurse midwife collected specimens for Pap smears from the ectocervix and endocervix using a plastic Ayres spatula and cytobrush, respectively. The spatula and cytobrush were then vigorously rinsed in vials containing PreservCyt® solution that were stored at room temperature for up to 2 weeks before being batch-transported to the United States for cytological analysis. After cervical specimens were collected, visual inspection with acetic acid (VIA) test and colposcopic exams were performed on all women by the nurse and gynecologist, respectively. If indicated by colposcopy or cytology results, lesions were further evaluated by biopsy, endocervical curettage, or loop electrical excision. Definitive surgical treatment (hysterectomy; *n*=2) was provided as necessary.

Laboratory tests

Cytological analyses were undertaken in the United States after batch transport of specimens from Zambia. Upon arrival, the specimen vials [prelabeled with a unique identifying number] were logged and processed with a ThinPrep® 3000 processor [24-26]. All slides were stained using the ThinPrep® Imaging System TP-3000 stain protocol. Slides had coverslips applied on the "Sakura Tissue-Tek® GLAS Automated Glass Coverslipper" and allowed to dry prior to review. All ThinPrep® samples were screened and diagnosed by a certified senior cytotechnologist according to the 2001 Bethesda System guidelines [15]: normal [no squamous cell abnormality], atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), and suspicious for squamous cell carcinoma (SCC). All abnormal slides and 10% of normals were subsequently reviewed by a board certified senior cytopathologist. We performed HPV typing using the Roche Linear Array® polymerase chain reaction (PCR) from the residual fluid in the specimen to test for the presence of genital HPV types [16]. The cytotechnician, cytopathologist, and lab technician conducting HPV assays were all blinded to the clinical profile and colposcopic and histological findings to ensure unbiased reporting.

Statistical analysis

Data entry was entered on site and confirmed in the United States. Statistical analysis was done using SPSS14.0 for Windows™ (SPSS, Inc. Chicago, IL) and Design package of R Version 2.1.1. We conducted univariate and multivariable logistic regression to identify sociodemographic and clinical characteristics predicting severe cytological abnormalities (defined as either HSIL or SCC). We did not want to necessarily assume a linear relationship between continuous predictors (age and CD4+ cell counts) and the log-odds of severe cytological abnormalities, so these continuous variables were initially fit using restricted cubic splines with 3 knots (using the default knot locations in the Design package). However, because there was little evidence suggesting a non-linear relationship between CD4+ cell count and the log-odds of severe cytological abnormalities (*p*>0.70), linearity was assumed for CD4+ cell counts in the models presented here. Because of the limited sample size, we included in the multivariable model only variables deemed a priori to be most scientifically important for predicting the presence of severe cytological abnormalities.

Results

Between July and September 2004, 150 HIV-infected women were recruited in this cross-sectional study. The median age was 36.0 years (range 23-49) and their median CD4+ cell count was 165.0/μL (range 7-942). 76.3% (114/148) women reported receiving antiretroviral

therapy whereas/although 22.9% (34/148) women had never accessed but were presently seeking antiretroviral therapy. About a third of the women (56/150, 37.3%) were married and cohabiting with their husband, just under a half of them were educated beyond high school (71/150, 47.3%) and a majority (87/143, 60.9%) had a family income of less than US$100 per month (~US $3/day). Little over a third (57/149, 38.2%) of the women reported their age of first sexual intercourse as less than 18 years and more than 85% of women reported between one and five lifetime sexual partners (120/142, 82.7%). Of the 150 women who were evaluated with cytological smears, only 10 (6.7%) had no abnormality whereas 140 (93.3%) were found to have a squamous cell abnormality. SCC was reported in 30 (20.0%), HSIL in 49 (32.7%), LSIL in 35 (23.3%), and ASC-US in 26 (17.3%) women on cytology (Fig. 1). In the univariate analysis, between those with or without severe cytological abnormalities, we found no statistical difference between educational status, marital status, having multiple ($\geq$6) lifetime sexual partners, and self-reported age of first sexual intercourse ($\geq$< 18 years, self-reported non-consistent/no condom use and nulliparity). However, women who had presence of high-risk types of HPV were 9.2 (2.6-32.8) times more likely to have HSIL and SCC cytology than women who did not have high-risk HPV types (p=0.001). Age was associated with the presence of cytological abnormalities (p=0.021); the odds of having severe cytological abnormalities were the highest at the median age of 36 (Fig. 2). CD4+ cell counts were linearly associated with the presence of HSIL/SCC lesions (p=0.027) and the odds ratio for a 100-count decrease in CD4+ count (e.g., the odds ratio for decrease from 300/μL to 200/μL) was 1.25 (95% CI of 1.03-1.54) (Fig. 3). Because of our sample size, we were limited in the number of variables we could include in the multivariable analysis [47]. We chose to include age (using restricted cubic splines with 3 knots), education, lifetime number of sexual partners (between 1 and 5, $\geq$6), age of first sexual intercourse (<18 or $\geq$18 years), CD4+ cell count, and presence of high-risk HPV types to develop a parsimonious multivariable model. Ten observations had missing data. On multivariable modeling, presence of high-risk HPV types was the only significant predictor of severe cytological abnormalities (adjusted OR: 12.4, 95% CI: 2.62-58.1, p=0.02) (Table 1).

Discussion

Nearly one in five HIV-infected women screened in our study had cytological evidence of squamous cell carcinoma and one in three had cytological evidence suggestive of HSIL. This high prevalence (>50%) of such severe cytologic abnormalities in women immunocompromised by HIV is particularly alarming given the fact that approximately 12-30% of immunocompetent HIV-negative women with untreated HSIL are known to progress to invasive cancer [17-19]. These results indicate the crucial importance of screening HIV-infected women who live in resource-constrained settings, like those in Zambia, who are now accessing antiretroviral therapy. The availability of cost-effective screening and treatment for women who live in these environments is critical to reducing the morbidity and mortality associated with cervical cancer.

Of the numerous cervical cancer screening studies that have been performed among HIV-infected women in industrialized settings, most have found significantly higher rates of preinvasive disease when compared to HIV-negative women [10-13,19-23]. In a review of cervical cytology in HIV-infected women residing in such environments, the overall reported prevalence of abnormalities ranged from 6% to 32%, with that of low-grade lesions ranging from 11% to 19% and high-grade lesions from 7% to 15% [46]. In the same review, prevalence rates of abnormal cervical cytology in HIV-infected women were reported to be as high as 38% greater than those in HIV-negative women.

In general, most studies of cervical cytology among HIV-infected African women have been based on opportunistic screening studies involving women attending outpatient clinics for general medical care. Overall, screening results from such populations have revealed a 2- to

3-fold increased risk of cellular abnormalities, and from such diverse sub-Saharan African settings as Zimbabwe [25,26], Kenya [27,28], Senegal [29,30], Malawi [31,32], Rwanda [33], Tanzania [34], Zaire [35], and South Africa [36 37]. The highest rates of cellular abnormalities reported to date from Africa have come from investigations of commercial sex workers in Zaire (27%) [35] and STI clinic attendees in Senegal (43%) [29]. In comparison, the overall abnormal cytology rate of 93.8% and ≥HSIL rate of 53.1% in our study are perhaps one of the highest reported in the literature for HIV-infected women.

The reasons for this high-prevalence could be partially attributed to the fact that the women in our study were severely immunosuppressed (median CD4+ count 165/μL). The participants were recruited from HIV-infected women attending the tertiary care hospital to receive antiretroviral therapy, and to be eligible for such treatment they had to meet the criteria of having a CD4+ count of <200/μL or have recently experienced some other AIDS defining illness. Although a majority of our study participants (78.2%) were already taking antiretroviral therapy, however, most had been taking it for less than 6 months. Nonetheless, settings such as Zambia will encounter increasingly high numbers of such immunosuppressed women who will now be accessing antiretroviral therapy. Providing cervical cancer screening and treatment services linked to HIV/AIDS care is one possible avenue to provide this much needed prevention intervention.

Another possible explanation for the high rate of severe cervical abnormalities detected in our study participants is the very high sensitivity of monolayer liquid cytology [38-40], in comparison to conventional cytology used in previously cited studies. Also, because the cytological analysis was conducted in a sophisticated laboratory in the United States, it may not be representative of developing country settings. Nonetheless, it highlights the hitherto underestimated prevalence rate, mostly due to the lower sensitivity of conventional cytology [41,42].

It is also important to note that most study participants were women living in marginalized circumstances of the society, that is, most were inhabitants of peri-urban "compounds" that are living quarters characterized by high unemployment rates, severe shortages of fresh water, poor housing, inadequate sewage, and high rates of infectious diseases. All of the above are widely prevalent conditions for the majority of HIV-infected women living in urban sub-Saharan African cities like Lusaka. These same socioeconomic conditions prevent them from accessing preventive and therapeutic clinical care, thereby increasing their vulnerability and putting them at double jeopardy for both HIV/AIDS and cervical cancer.

As seen in our results, the risk of severe cytological abnormalities was highest around the median age of our participants (36 years) with a downward trend both above and below the median (Fig. 2). Because our sample was highly representative of HIV-infected women seeking antiretroviral therapy in the public sector clinics in Zambia, it strongly suggests the critical need for undertaking a concerted effort towards the provision of a cervical cancer screening and treatment program that benefits the average woman accessing these clinics.

Presence of high-risk HPV was an independent predictor of HSIL and SCC on multivariable modeling. These findings confirm the need for exploring the use of alternative screening methods like HPV testing in conjunction with cytology or low-cost visual inspection based methods, as a triage tool for the better management and adequate referral of these women to colposcopy and/or treatment. The use of HPV testing among HIV-infected women has been controversial [43-45]; however, the use of HPV testing in this high-risk population may offer better outcomes if cost of testing falls within the range of donor-funded or government supported activities. The crucial importance of investigations to study the natural history of HPV-induced cervical neoplasia and the impact of antiretroviral therapy on the natural history

of cervical neoplasia in these women is also highlighted through the findings of this preliminary study.

Bilateral and multilateral donor assistance programs (e.g., Presidents Emergency Plan for AIDS Relief, Global Fund) are improving the availability of antiretroviral therapy in resource-constrained settings [8,9]. The findings in this report highlight the importance of linking cervical cancer prevention services for HIV-infected women to antiretroviral therapy programs. By so doing, we have the opportunity to reduce the burden of both HIV and cervical cancer in impoverished settings where both diseases are most prevalent.

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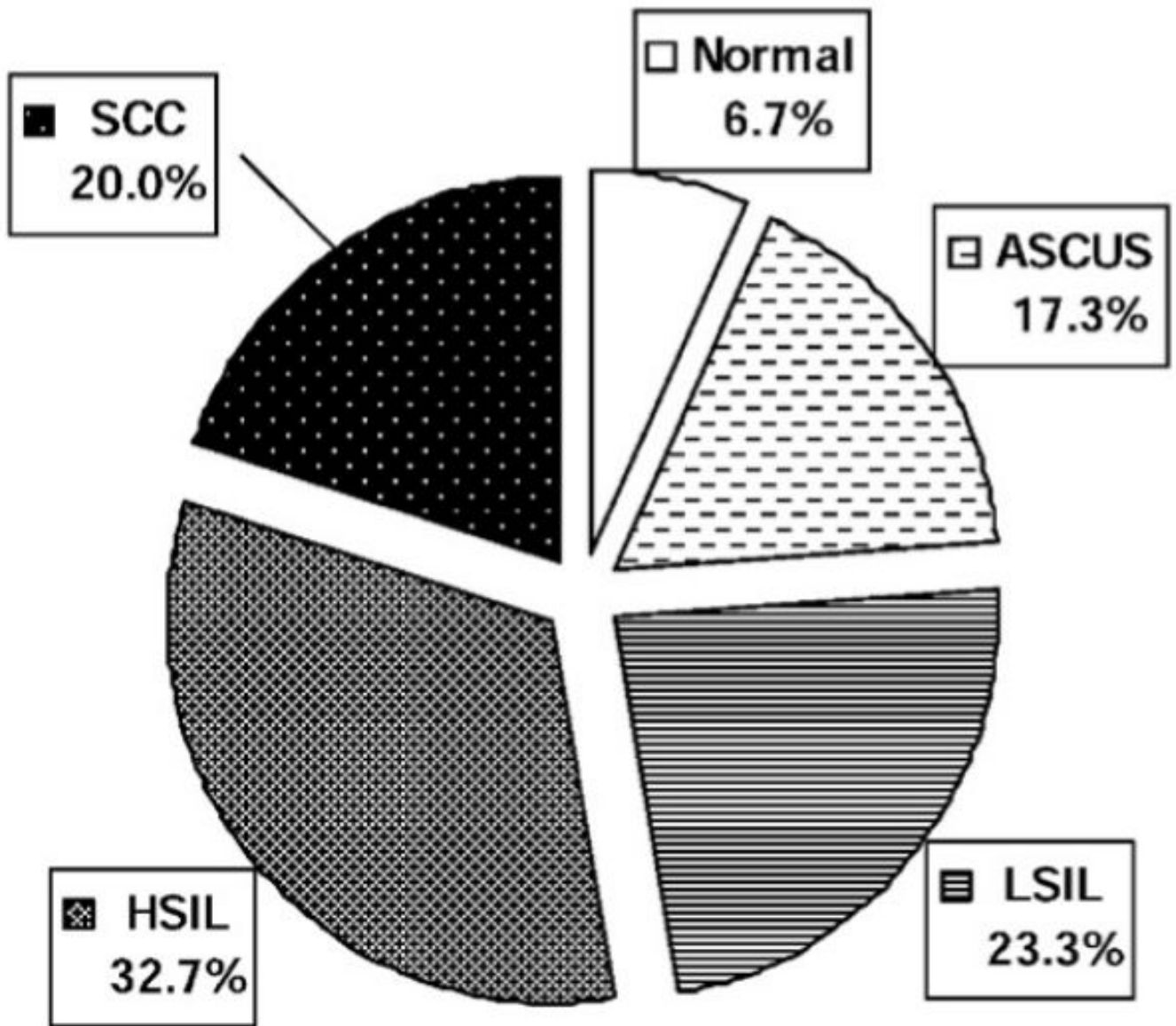
Fig. 1.
Cytological results on ThinPrep Pap test among 150 HIV-infected women in Zambia. Note: ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: highgrade squamous intraepithelial lesions; SCC: suggestive of squamous cell carcinoma.
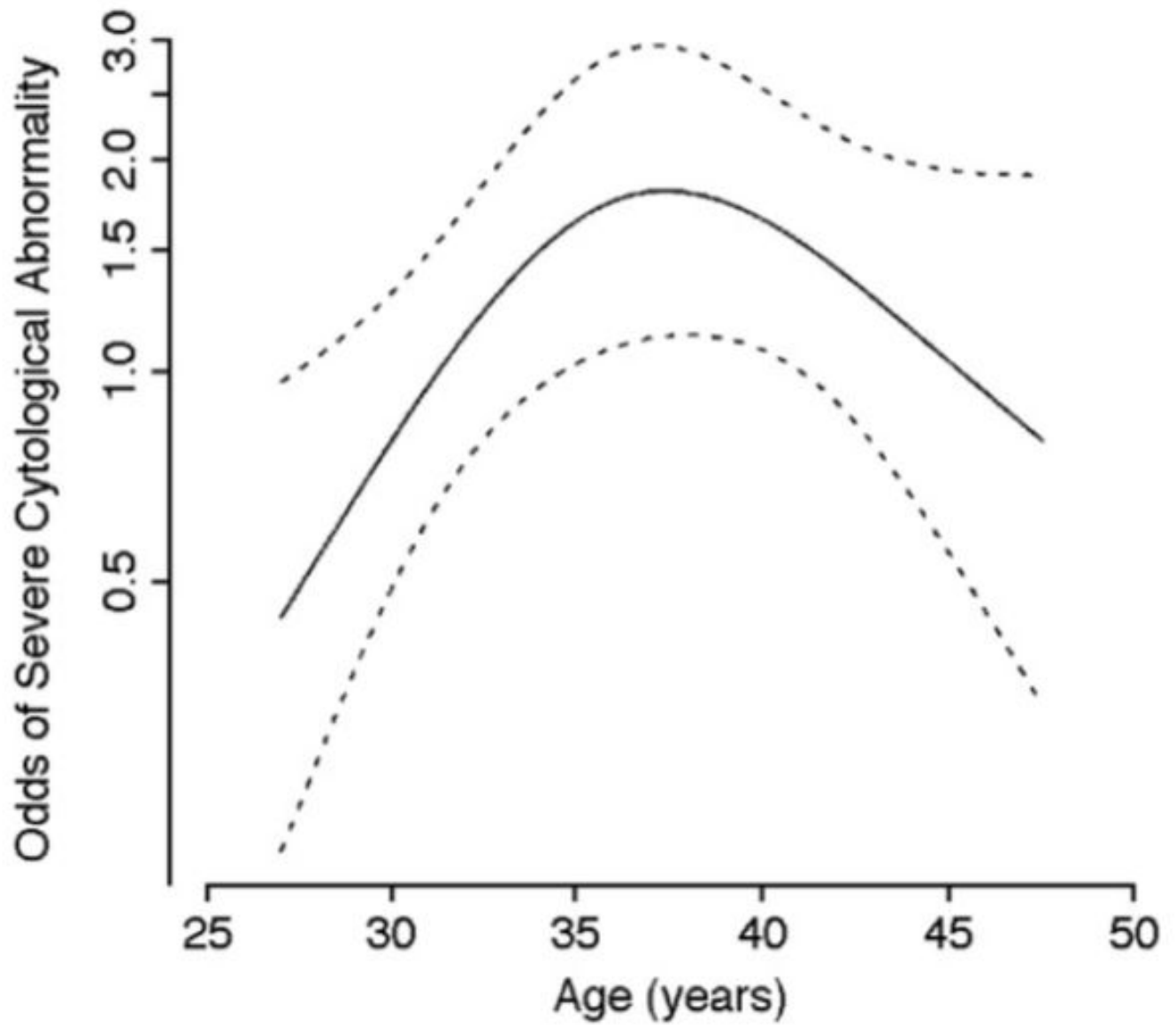
Fig. 2.
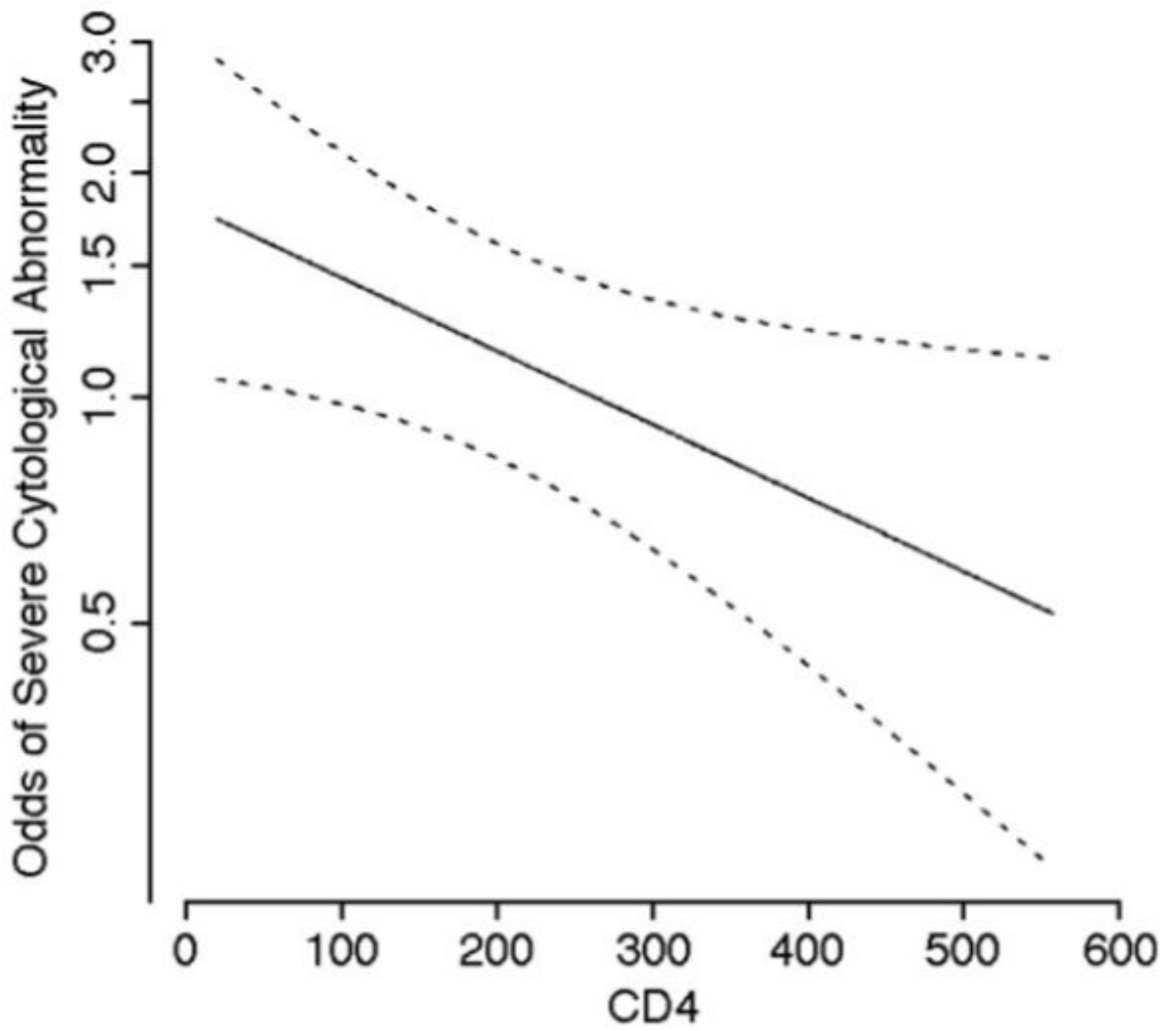Relationship between age of participants and presence of severe cytological abnormalities.

Fig. 3.
Relationship between CD4+ cell counts and presence of severe cytological abnormalities.

Table 1

Univariate and multivariable logistic regression analysis for the predictors of severe cytological abnormalities

Variable	Univariate analysis		Multivariable analysis	
	OR [95% CI]	p value	Adjusted OR [95% CI]	p value
Age [n=150][a]				
36 vs. 30 years	2.21 [1.25-3.90]	0.021	2.03 [1.08-3.81]	0.07
36 vs. 45 years	1.70 [0.76-3.81]		1.87 [0.75-4.63]	
Education [n=150]				
No/some school education	0.67 [0.35-1.29]	0.24	0.77 [0.36-1.65]	0.50
>High school education	1		1	
Marital status [n=150]				
Unmarried/non-cohabiting	1.18 [0.61-2.30]	0.61	-	
Married: cohabiting	1			
Family income [n=143]				
<$100/month	0.56 [0.28-1.11]	0.10	-	
≥$100/month	1			
Lifetime number of sexual partners [n=145]				
1-5 lifetime partners	0.98 [0.42-2.40]	0.98	0.97 [0.35-2.68]	0.95
≥6 lifetime partners	1		1	
Age at first intercourse [n=149]				
Below 18 years	1.01 [0.52-1.97]	0.96	1.16 [0.50-2.70]	0.72
18 years or above	1		1	
Condom use [n=147]				
Non-consistent/never used	0.94 [0.44-2.00]	0.889	-	
Consistent user	1			
Parity [n=141]				
Nulliparity	0.61 [0.24-1.56]	0.30	-	
1 birth or more	1			
CD4+ count [n=145][b]				
Each 100 count decrease [e.g., 100 vs. 200/μL]	1.25 [1.03-1.54]	0.027	0.88 [0.70-1.10]	0.26
Presence of high-risk HPV [n=150]				
HR HPV present	9.25 [2.60-32.88]	0.001	12.4 [2.62-58.1]	0.002

Variable	Univariate analysis		Multivariable analysis	
	OR [95% CI]	p value	Adjusted OR [95% CI]	p value
HR HPV absent	1		1	

[a] Because of a significant non-linear relationship between age and the odds of severe cytological abnormalities [$p<0.05$, see Fig. 2], the odds ratio for two different age comparisons are shown.

[b] There exists a significant linear relationship between CD4+ cell count and the odds of a severe cytological abnormality [see Fig. 3].