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Risk Factors of High Grade Squamous Intraepithelial Lesions of Cervix in HIV Infected Women at Khon Kaen Hospital

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ABSTRACT

Objective: To determine risk factors associated of high grade squamous intraepithelial lesion (HSIL) in HIV infected women.

Material and Methods: Retrospective cohort study of 250 HIV infected women registered in colposcopy clinic at Khon Kaen Hospital between January 1st 2008 and January 1st 2014 who had high grade histology (HSIL) was conducted. Risk factors associated with HSIL histology were studied between HSIL and low grade squamous intraepithelial lesion (LSIL) plus normal histology group. Risk factors were analyzed by logistic regression and recurrence of HSIL was analyzed by survival analysis.

Results: The colposcopic records of 250 HIV infected women were analyzed. Mean age was 36.0 ± 7.5 years, and the mean CD4 cell count was 391.0 ± 229.3 cell/μL. Age ≥ 35 years was only significant risk factor associated with HSIL histology in HIV infected women (RR 2.06, 95% CI = 1.17 - 3.63). There were 32 (29.4%) and 7 (5.0%) women in HSIL and LSIL group had recurrent of HSIL histology respectively. Median time to recurrence of HSIL group compared with LSIL group was 55.6 months versus 59.8 months ($p < 0.05$).

Conclusion: Age ≥ 35 years was a risk factor of HSIL histology in HIV infected women. Higher recurrence of HSIL was found in HSIL group.

Keywords: HSIL, HIV infected women, Risk factor

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Introduction

Thailand is one of endemic areas for HIV infection. Cervical cancer is the most common AIDS-related malignancy[1] because of highly prevalence of human papillomavirus (HPV) infection[2,3]. The prevalence of cervical intraepithelial lesion (CIN) in HIV-infected women was estimated as high as 20-40%[4,5]. Persistent infection with high-risk oncogenic

types of HPV is required for the development of high-grade lesions that may progress to invasive cervical cancer[6-8]. Progress of CIN to invasive cervical cancer in women with HIV infection was more rapidly[9-11].

According to the prevent cervical cancer guideline of The US Public Health Service (USPHS) and The Infectious Disease Society of America (IDSA) recommended all HIV infected women should have a Pap smears in every 6 months (Semi-annual Pap smear screening). If results of both are normal, annual cytological screening is suggested. In HIV infected woman increased persistence of genital HPV infection due to immunocompromised state and that cervical lesions are more likely to progress to high-grade lesions[6-8]. Some reports of initiation of HAART are beneficial to reduced prevalence of persistence HPV infection and progressive to high grade squamous intraepithelial lesion (HSIL)[12].

There were several factors that might be associated with CIN in HIV-infected women, especially in those who had HSIL[6-8,11,12]. The present study aimed to determine risk factors that related with HSIL in HIV infected women.

Material and Methods

The study design was retrospective cohort study. The study protocol was approved by the Khon Kaen Hospital Institute Review Board in Human Research. Colposcopic records registered in colposcopy clinic at Khon Kaen Hospital between January 1st, 2008 and January 1st, 2014 were reviewed. HIV-infected women with HSIL, low grade squamous intraepithelial lesion (LSIL) or normal histology were included. Previous history of gynecologic cancer was excluded. Histology was performed by excisional procedures (Loop electrosurgical excision procedure (LEEP), colposcopically directed biopsy (CDB) followed by LEEP in case of HSIL. All cases were margins negative after one or repeated LEEP. Sample size was calculated by using risk factor of HSIL from Araujo[11], 102 women were needed for study with 10% of difference in estimated size and significant level at 0.95. Baseline characteristics including age, number of parity, menopausal status, age at first sexual intercourse (SI), history of sexually transmitted diseases (STD), smoking, oral contraceptive pills (OCPs) users (regularly used OCPs at least 3 months before underwent colposcopy), number of sexual partner, CD4 cell count and used antiretroviral drugs were reviewed. Time to recurrent (time from negative surgical margin to new abnormal cytology detected) and result of histology of recurrence were also recorded. Follow up cytology schedules of normal and LSIL histology were every 6 months and HSIL was every 4 months.

Continuous variables were analysed using student's t-test and categorical variables were analyzed by Chi-square test. Regression analysis was used to analysed risk factors. Recurrent rate of HSIL and LSIL group was analysed by survival analysis. The statistical analysis was performed by SPSS 19.0. P-value less than 0.05 was considered statistically significance.

Results

Two hundred and fifty HIV infected women who had abnormal Pap smear and referred to colposcopy clinic consisted of atypical squamous cell of undetermined significance (ASCUS) 15.6%, atypical squamous cell cannot exclude HSIL (ASC-H) 2%, LSIL 48.1%, HSIL 28.8%, squamous cell carcinoma 3.6%, atypical glandular cell not otherwise specified (AGC-NOS) 0.8% and adenocarcinoma 1.2%. Of these, 109 women were HSIL histology and 141 women were LSIL and normal histology. The median age was 36.0 ± 7.5 years, mean CD4 cell count was 391.0 ± 229.3 cell/μL. Table 1. show characteristic of participants. Baseline characteristics were similar except history of sexual transmitted disease.

Table 1. Characteristics of HIV infected women.

Characteristic	HSIL (n)	LSIL and Normal histology (n)
Age (yrs), mean ± SD	37.0 ± 6.5	35.5 ± 7.5
Age < 35 yrs	64 (45.3)	36 (33.0)
Age ≥ 35 yrs	77 (54.7)	73 (77.0)
Parity, n (%)		
Nulliparity	21 (19.3)	23 (16.3)
Multiparity	88 (80.7)	118 (83.4)
Sexual partner, n (%)		
Single	48 (44.0)	66 (46.8)
Multiple	61 (56.0)	75 (53.2)
Age of 1st SI (yrs), n (%)		
< 20	75 (68.8)	92 (65.2)
≥ 20	34 (31.2)	49 (34.8)
Smoking, n (%)		
No	103 (94.5)	136 (96.5)
Yes	6 (5.5)	5 (3.5)
Antiretroviral drugs, n (%)		
No	51 (46.7)	66 (26.4)
Yes	58 (53.3)	75 (30.4)
OCPs users, n (%)		
No	104 (95.4)	139 (55.6)
Yes	5 (4.6)	2 (0.8)
Menopausal status, n (%)		
No	103 (94.5)	129 (91.5)
Yes	6 (5.5)	12 (8.5)
History of STDs, n (%)		
No	102 (93.6)	140 (99.3)
Yes	7 (6.4)	1 (0.7)
CD4 cell count, n (%)		
< 350 cell/μL	32 (54.2)	34 (45.3)
≥ 350 cell/μL	27 (55.8)	41 (54.7)

SI, sexual intercourse; OCPs, oral contraceptive pills; STD, sexual transmitted disease

Risk factors of HSIL were shown in Table 2. Only age ≥ 35 years was the independent risk factor of HSIL (RR 2.06, 95% CI = 1.17 - 3.63, p = 0.01) and no significant difference in other factors.

At 69 month of follow up period, proportion of recurrent rate in women with HSIL histology was significantly higher than in LSIL plus normal group (29.4% and 5%, p < 0.05). Time to recurrence was 55.61 months in HSIL group and 59.80 months in LSIL and normal histology group (p < 0.05). Most of recurrent cases in HSIL group were high grade histology and low grade histology in LSIL group. (Fig. 1.)

Table 2. Logistic regression analysis of risk factors for HSIL among HIV infected women.

Risk factors	RR (95% CI)	P
Age ≥ 35years	2.06 (1.17-3.63)	0.01
Multiparity	0.76 (0.37-1.56)	0.06
Multiple partner	1.06 (0.62-1.80)	0.82
Age of 1st SI < 20 years	0.76 (0.43-1.36)	0.37
Smoking	0.91 (0.21-3.85)	0.90
Antiretroviral drugs	0.96 (0.56-1.66)	0.90
OCPs users	3.36 (0.52-22.16)	0.20
Menopausal status	0.53 (0.18-1.52)	0.05
History of STDs	8.37 (0.95-73.19)	0.32
CD4 cell count < 350 cell/μL	1.22 (0.58-2.55)	0.59

SI, sexual intercourse; OCPs, oral contraceptive pills; STD, sexual transmitted disease

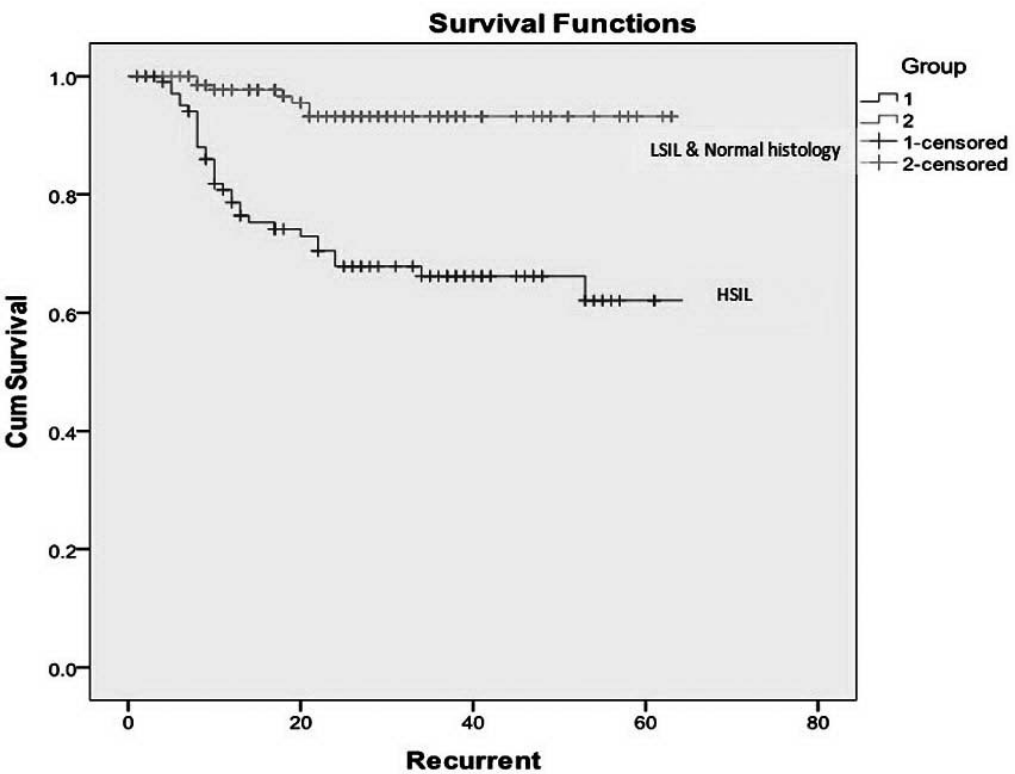

Fig. 1. Kaplan-Meiur curve of woman who HSIL compared with LSIL and normal colposcopic results.

Discussion

Cervical cancer is the most common gynecologic cancer in HIV infected women, especially in those who had persistent HPV infection. To our knowledge, factors that play the role in promotion of persistent HPV infection in general population are early sexual intercourse, multiple sex partners, smoking, high parity and immunocompromised host. For HIV infected women, there are additional factors that might affect on severity of intraepithelial lesion. The result of mean age of participants was 36.0 ± 7.5 years, consistent with most common period of the peak incidence of CIN between at 25-40 years of age[13]. We also found that women at age > 35 years old had HSIL histology significantly more than those at age < 35 years old. This finding might explain from long precancerous stage. But inconsistent with Araujo et al[11], they found that CIN was lower in women who older than 35 years. Nulliparity showed 30% reduction of HSIL histology, although without statistically significance. In case of multiparity, particular in those with history of vaginal delivery had more chance to have HPV infection due to repeated trauma during delivery. For number of sexual partner, we found that the incidence of HSIL histology was not significant difference between single and multiple partners which was consistent with Araujo at el[11]. They compared the impact of the lifetime sexual partners on the incidence of CIN and found that lifetime sexual partner more than 3 or less had no significant difference. Nowadays, age at first SI tend to decrease from the past decades. Women who had early SI take high risk in HPV infection because of longer period of HPV exposure, those with HIV infection in particular. This study found that HIV infected women who had SI before age of 20 had more incidence of both HSIL and LSIL histology but no statistically significance. The previous study of Araujo et al showed cut-off age at first SI at 19 years old and revealed that women who had SI before 19 years old had 2.4 times higher risk of CIN than after 19 years old. This is possible that the young women who had early SI had injured of cervical epithelium during SI earlier than the elders, therefore the sexually transmitted diseases including HPV or HIV could infected via this injured cervical epithelium. In endemic area of HIV infection such as Africa, prevalence of HSIL was as high as 53.1% and of these, the average CD4 cell count was 165 cells/μL[14]. Low CD4 cell count was found to relate with high prevalence of HPV infection and CIN in cytologic screening[15-20], especially in young women and women with high HIV viral load. In some studies founded that CD4 cell count lower than 200 cells/μL was the strongest predictor of an abnormal Pap smear[21,22]. In our setting, we use the same cut-off level of CD4 cell count at 350 cells/μL as the Ministry of Public Health initiated antiretroviral drug (HAART regimen). Only half of HIV infected women in our study had CD4 cell count records because some HIV infected women were treated at other hospitals and CD4 cell count records were not accessible. However, form the available data, women with CD4 cell count > 350 cell/μL had tendency to have less HSIL histology. CD4 cell count had a little effect on the risk of CIN in one study[20]. Cigarette smoking (first or second hand smokers) was associated with CIN[23]. Most of Thai women and their spouses were not smokers. Therefore, the numbers of smoking HIV infected women in this study were low, and too small to determine the difference among groups. Antiretroviral drug (HAART regimen) was provided in all patients with CD4 cell count less than 350 cells/μL in our institute. Antiretroviral drugs can reverse weakening of the immune response and regain protection against cervical dysplasia[11]. Moreover, antiretroviral drugs protected against LSIL progression[24] However, the current study showed no significant difference in risk of HSIL between two groups. It is possible that women who did not receive antiretroviral drugs had CD4 cell count ≥ 350 cells/μL. Contraceptive methods used in our participants were condom, oral contraceptive pills and tubal resection. Most of them had tubal resection. Only 7 in 250 women took oral contraceptive pills. Women who used oral contraceptive pills had risk of HSIL 3.3 times of women who did not, but no statistically difference was detected because the number of HIV infected women who preferred this method was small. From reanalysis of

24 epidemiological studies in 2007 reported the risk of using oral contraceptive pills and cervical cancer, adenocarcinoma in particular and the duration of use is also play an important role[25]. However, this hypothesis was inconsistently supported[26,27]. Postmenopausal women with HIV infection in the present study were 18 in 250. Only 6 of 109 (5.8%) of postmenopausal women in the present study had HSIL histology. Four of them had previous HSIL, one had squamous cell carcinoma and one had LSIL cytology whereas 12 of 141 women had LSIL histology. Three quarter of them had previous low grade cytology (atypical squamous cell of undetermine significance, ASCUS and LSIL). This finding showed consistent of cytology and histology of this age group. Postmenopausal women with HIV infection are the minority in HIV infected population, therefore, reflected the small proportion of abnormal histology. Despite minority but showed borderline significant of HSIL histology. Although we found that women who had history of other STDs had 8.3 times increase risk of HSIL but no statistically significance was observed. The information about other STD infection came from history taking alone and we did not investigate the co-infection unless suspected evidence was found. Lehtovirta et al[20] reported the association between bacterial vaginosis (BV) and CIN. They found significant greater risk of CIN in BV infection women. However, this association was inconsistent with Platz- Chistiansen et al[28] who found only 1.4% of BV infection in women with CIN compared to 5% of non CIN.

Recurrence rate of CIN was 29.4% in HSIL group when compared to 5.0% of LSIL group. This was similar to the previous studies which reported that the recurrent of CIN after excisional treatment range from 20-75%[29-32]. Prospective study showed that spontaneous regression rate of LSIL was 60-80% and regressions typically occur in 2 years follow-up[31]. Recurrent of CIN was double in women who had CD4 cell count ≤ 350 cells/μL in the present study. The possible explanation was low immunity in women who had low level of CD4 cell count increase risk of HPV persistent infection and development of CIN after exposed to new HPV infection. Grade of recurrent lesion was mostly similar to prior lesion. Surgical margin status was not affect our results because of all cases were margin negative. Time to recurrence was longer than 50 months in both groups. This long lesion-free interval in this study reflected the adequate treatment in our institute.

The strengths of our study were firstly, long follow-up period which allowed us to analyse the recurrence rate of CIN in our setting. Secondly, we used histological confirmed of CIN. Lastly, lost to follow-up rate in our study was low.

The limitations of our study were retrospective study, made it difficult to gain the complete data, especially CD4 cell count, onset and type of antiretroviral drugs used, HIV viral load and duration of HIV infection. HPV testing was not available for routine screening or test of cure strategy.

In conclusion, age of women ≥ 35 years was a risk factor for HSIL in HIV infected women. Recurrent rate in HSIL histology was higher than in LSIL histology group.

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ปัจจัยเสี่ยงของรอยโรคปากมดลูกขั้นสูงในสตรีที่ติดเชื้อเอชไอวี

กฤติยา โสมะเกษตรินทร์, ทุมวดี ตั้งศิริวัฒนา, วีรพล ศรีนิล

วัตถุประสงค์: *เพื่อศึกษาว่าปัจจัยเสี่ยงที่มีความสัมพันธ์กับรอยโรคปากมดลูกขั้นสูงในสตรีที่ติดเชื้อเอชไอวี*

วัสดุและวิธีการ: *เป็นการวิจัยเชิงพรรณนาแบบย้อนหลัง ศึกษาในสตรีติดเชื้อเอชไอวีจำนวน 250 คน ที่มีผลพยาธิสภาพวิทยาเป็นรอยโรคปากมดลูกขั้นสูง ที่เข้ารับการรักษาที่คลินิกคอลโปรสโคป โรงพยาบาลขอนแก่น ระหว่างวันที่ 1 มกราคม พ.ศ.2551 ถึง 1 มกราคม พ.ศ.2557 ศึกษาปัจจัยเสี่ยงของรอยโรคปากมดลูกขั้นสูงเปรียบเทียบกับกลุ่มที่มีรอยโรคปากมดลูกขั้นต่ำ และผลพยาธิวิทยาปกติ ใช้การวิเคราะห์ปัจจัยเสี่ยงแบบ logistic regression ร่วมกับศึกษาอัตราการกลับเป็นซ้ำของรอยโรคปากมดลูกขั้นสูงโดยใช้ survival analysis*

ผลการศึกษา: *สตรีที่ติดเชื้อเอชไอวี 250 คน มีอายุเฉลี่ย 36.0 ± 7.5 ปี และมีค่าเฉลี่ยของ CD4 cell count 391.0 ± 229.3 cell/μL และการศึกษาปัจจัยเสี่ยงพบว่าอายุมากกว่าหรือเท่ากับ 35 ปี เป็นปัจจัยเสี่ยงของรอยโรคปากมดลูกขั้นสูง (RR 2.06, 95% CI = 1.17-3.63) และพบว่าผู้ป่วย 32 ในกลุ่มรอยโรคปากมดลูกขั้นสูง และ 7 คนในกลุ่มรอยโรคปากมดลูกขั้นต่ำ มีการกลับเป็นซ้ำ โดยค่าเฉลี่ยของการกลับเป็นซ้ำในรอยโรคปากมดลูกขั้นสูงเทียบกับรอยโรคปากมดลูกขั้นต่ำคือ 55.6 และ 59.8 เดือน (P<0.05)*

สรุป : *อายุมากกว่าหรือเท่ากับ 35 ปี เป็นปัจจัยเสี่ยงของรอยโรคปากมดลูกขั้นสูงในสตรีที่ติดเชื้อเอชไอวี และการกลับเป็นซ้ำพบมากในกลุ่มที่มีรอยโรคปากมดลูกขั้นสูง*