Original Article

Cervical Cancer in Women with Squamous Cell Carcinoma Cytology

Noonlamtong K, MD[1], Temtanakitpaisan A, MD[1], Kleebkaow P, MD[1], Aue-aungkul A, MD[1], Chumworathayi B, MD[1], Luanratanakorn S, MD[1], Kietpeerakool C, MD[1]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: To determine the rate of cervical cancer among women with squamous cell carcinoma (SCCA) cytology, as well as its associated risk factors. The results were pooled with previously reported findings.

Materials and Methods: The authors reviewed data regarding women with SCCA cytology that underwent colposcopy at Khon Kaen University's Srinagarind Hospital between October 2008 and March 2016. A meta-analysis was performed to incorporate the present study and the previous studies retrieved from a bibliographic database search to provide the pooled rate of cervical cancer among women with SCCA cytology. A random-effects model was applied for meta-analysis.

Results: The data of 69 patients were reviewed. After colposcopy, 64 patients underwent cervical conization and/or hysterectomy, and the five remaining patients underwent colposcopically-directed biopsy only. Thirty-six patients (52.2%; 95% CI 40.1 to 64.3) were found to have invasive lesions, all of them were cervical cancer. There were no significant associations between the patients' age, level of education, menopausal status, parity status, infection with human immunodeficiency virus, or symptoms presented during the cervical smear and the rate of invasive cervical cancer. After combining the data from the present study with the data from six other eligible studies, which were retrieved from the search of standard bibliographic databases, the pooled rate of cervical cancer among women with SCCA cytology was 56% (95% CI 36 to 77).

Conclusion: Approximately, half of women with SCCA cytology in the present study harbored cervical cancer. No significant factors predicting underlying cervical cancer were noted. By means of meta-analysis, the pooled rate of cervical cancer among women with SCCA cytology was 56%.

Keywords: Cervical cytology, Squamous cell carcinoma, Risk factor, Meta-analysis

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Although, there are modern cervical cancer screening methods that carry a considerably high diagnostic performance, including the high-risk human papillomavirus (HR-HPV) test and HPV genotyping, cervical cytology remains the principal method for cervical cancer screening in the developing world where nearly 90% of cervical cancer deaths occur[1].

The characteristics of cervical cytology reflect the risk of encountering significant cervical pathology[2]. Squamous cell carcinoma (SCCA) cytology is the most severe squamous cell abnormality. SCCA cytology denotes cases in which there are dysplastic squamous epithelia with marked variation in cellular size and shape. The nuclei of these cells also vary markedly in size and contain an irregular arrangement of coarsely clumped chromatin. Abnormal cell forms, such as tadpole cells or spindle cells, are typical in cases of non-keratinizing SCCA[2]. In addition, a tumor diathesis, which is defined by a cervical smear background containing necrotic debris and old blood, is usually identifiable, particularly in cases of non-keratinizing SCCA[2].

SCCA cytology is extremely rare, with reporting rates of less than 0.1%[2,3]. Women with SCCA cytology carry an immense risk of having cervical cancer. The present study was conducted to evaluate the rate of invasive cervical cancer among women with SCCA cytology, as well as its associated risk factors.

Correspondence to:

Kietpeerakool C.

Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-81-5935700

Email: kiet_ji@hotmail.com

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Previous studies evaluating the rate of invasive cancer among women with cervical smears suggesting SCCA were searched and the results were pooled with our findings by means of meta-analysis.

Materials and Methods

After receiving approval from the Research Ethics Committee, the authors retrieved data from the Colposcopy Database and Surgical Pathology Database regarding women with SCCA cytology undergone colposcopy at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand between October 2008 and March 2016. Because of the rarity of SCCA cytology, this study included all consecutive women who had this smear abnormality during the study period to obtain a largest sample size as possible. Abstracted data included baseline characteristics, colposcopic findings, subsequent management, and detailed histopathologic results. Pregnant women were excluded from the present study.

Colposcopic examination was performed following the application of 5% acetic acid solution on the upper vagina and cervix. Colposcopy and subsequent management were carried out by gynecologic oncology trainees under direct staff supervision. Grading of the severity of colposcopic findings was based on the density of acetowhite epithelial changes, sharpness of the lesion margins, and abnormal and atypical vascular patterns. The final histological diagnosis was made based on the most severe histological results after initial colposcopy. All patients had their pathological materials initially reported or reviewed by a gynecologic pathologist (Kleebkaow P). Invasive cervical cancer was clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO)[4].

Statistical analysis was performed using Stata version 10. Descriptive statistics were used for reporting demographic data, detection rate of underlying invasive lesions, and detailed histology of cancers. A 95% confidence interval (CI) of the rate of invasive cancer was calculated to determine the precision of the data. The associations between clinical variables such as age, level of education, menopausal status, status of HIV infection, and presenting symptoms and the incidence rate of invasive lesions were assessed using a Chi-square and Fisher's exact test when appropriated. A p-value of less than 0.05 was considered to be statistically significant.

The incidence rate of invasive lesions found in the present study was pooled with previously reported findings using proportion meta-analysis. A random-effects model was applied in the meta-analysis using the method described by DerSimonian and Laird[5]. The authors regarded heterogeneity as substantial if I^2 is greater than 50% and there is a low p-value (less than 0.10) in a Chi-square test for heterogeneity.

To find previous studies on this topic, the authors electronically searched Ovid Medline, Scopus, and Web of Science databases in April 2017, using combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "cervical smears", "vaginal smears", and "squamous cell carcinoma". The search was restricted to reports written in English. Reference lists of relevant articles were manually searched for additional reports. All relevant articles were identified on PubMed and the authors made a further search for newly published articles using the 'related articles' feature.

Results

Findings of the present study

Data from 69 patients with SCCA cervical cytology were reviewed. The mean age of the patients was 49.6 years. Table 1 shows the baseline characteristics of the patients, the majority of whom (n = 65, 94.2%) were multiparous. Nine (13.0%) women had pre-existing symptoms at the time the smears were taken including abnormal vaginal discharge (n = 6), vaginal discharge (n = 2), and pelvic pain (n = 1). Almost all the cervical smears in the present study were conventionally prepared (n = 66).

After colposcopy, 64 patients underwent cervical conization and/or hysterectomy, and the five remaining patients underwent colposcopically-directed biopsy only. The final histological diagnoses of 69 patients included invasive cervical cancer (n = 36; 52.2%; 95% CI 40.1 to 64.3), cervical intraepithelial neoplasia (CIN) II-III (n = 29, 42.0%), CIN I (n = 3, 4.4%), and cervicitis (n = 1, 1.5%). Of the 36 patients with invasive cervical cancer, 34 (94.4%) had SCCA and the remaining two had adenocarcinoma. The FIGO staging classifications of the 36 women with invasive cervical cancer were stages IA1 (n = 18), IA2 (n = 3), IB1 (n = 5), IIA (n = 3), IIB (n = 6), and unknown (n = 1).

There were no significant associations between the patients' age, level of education attainment, menopausal status, infection with human immuno-deficiency virus (HIV), or symptoms presented during the cervical smear and the rate of invasive cervical cancer (Table 2).

Table 1. Demographic characteristic of the patients

Patient characteristics	n (%)
Age (years)	
21 to 40	11 (15.9)
41 to 50	26 (37.7)
51 to 70	32 (46.4)
Menopausal status	
Premenopausal	37 (53.6)
Postmenopausal	32 (46.4)
Educational attainment	
Primary education	52 (75.4)
Secondary education	6 (8.7)
Bachelor of higher	11 (15.9)
HIV infection status	
Negative	63 (91.3)
Positive	6 (8.7)
Parity status	
Nulliparous	4 (5.8)
Multiparous	65 (94.2)
Current contraception	
None	26 (37.7)
Tubal resection	31 (44.9)
Oral combined pills	8 (11.6)
Depot medroxyprogesterone acetate	2 (2.9)
Intrauterine device	1 (1.5)
Implant	1 (1.5)
Symptoms	
None	60 (86.9)
Vaginal bleeding	6 (8.7)
Leucorrhea	2 (2.9)
Pelvic pain	1 (1.5)

HIV=human immunodeficiency virus

Table 2. Factor predicting of underlying cervical cancer

Variables	Number of women with cervical cancer (n = 36) n (%)	p-value
Age (years)		
<35 (n = 5)	4 (80.0)	0.35
≥35 (n = 64)	32 (50.0)	
Educational attainment		
Primary education (n = 52)	29 (55.8)	0.29
Secondary education or higher (n = 17)	7 (41.2)	
Menopausal status		
Premenopausal (n = 37)	19 (51.4)	0.88
Postmenopausal (n = 32)	17 (53.1)	
HIV status		
Negative (n = 63)	33 (52.4)	0.91
Positive (n = 6)	3 (50.0)	
Symptoms		
Asymptomatic (n = 60)	30 (50.0)	0.48
Present (n = 9)	6 (66.7)	

HIV=human immunodeficiency virus

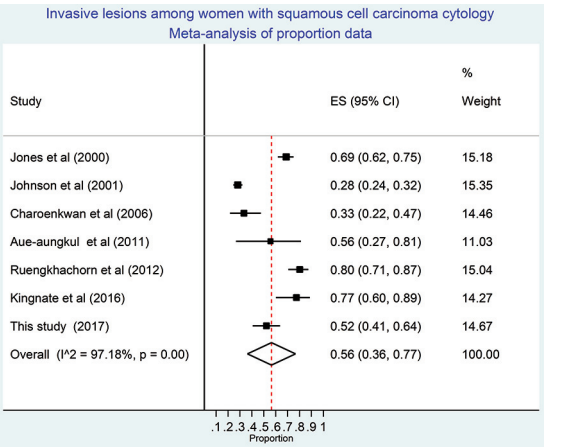

Figure 1. Meta-analysis of the rates of invasive cervical cancer among women with SCCA cervical smears.

Findings of meta-analysis

A bibliographic database search identified six eligible studies that evaluated the underlying pathology among women with SCCA cytology[3,6-10]. The total study population of the seven studies examined (the six mentioned above and the present study) consisted of 942 women. The rate of cervical cancer among women with SCCA cytology in the literature varied widely (from 28% to 80%). Figure 1 displays the results of the meta-analysis, which pooled the rate of cervical cancer observed in the present study with those of six previous reports. Overall, the pooled occurrence of underlying cervical cancer among women with SCCA cytology was 56% (95% CI 36 to 77).

Discussion

In the present study, the authors evaluated the occurrence rate of underlying invasive lesions among women with smears showing SCCA, as well as its associated risk factors. The frequency of invasive lesions was high (52.2%) and all were invasive cervical cancer. However, there were no clinical variables associated with the occurrence of invasive cervical cancer identified in the present study. Through meta-analysis of seven eligible studies (including the present study), the authors found the pooled rate of underlying cervical cancer among women with smears indicating SCCA was 56% (Figure 1).

A previous study observed that HIV-infected women who had abnormal cervical smears were a population subset with elevated risk of having significant lesions. This was particularly the case among women with smears indicating atypical squamous cells (ASC) and low-grade squamous intraepithelial lesions (LSIL)[11]. In the present study, the risk of underlying invasive lesions among women with smears indicating SCCA was not significantly affected by the patients' HIV infection status. However, the authors could not confidentially conclude these findings were accurate due to the limited number of HIV-infected women in the present study.

One of the cytological features that serves as a warning for underlying invasive cervical cancer is a tumor diathesis, which is indicated by a smear background composed of inflammatory cells, necrotic materials, and old blood[2]. As smear preparation using a liquid-based technique can attenuate the presence of a tumor diathesis in the background[2], there is the possibility that techniques for preparing cervical smears might affect the estimated risk of underlying cervical cancer among women with cervical smears suggesting SCCA. To the authors' knowledge, there has been no previous study determining the impact of smear preparation techniques on the estimated risk of cervical cancer among women with SCCA cytology. The association between smear technique and rate of underlying invasive lesions could not be determined in the present study due to the limited number of women with liquid-based smears. However, in a study by Uyar et al[12], conducted to evaluate the predictive values of cervical smears reported as malignant, both liquid-based and conventional cervical smears provided similar positive predictive values.

The focus of the meta-analysis carried out in the present study was the pooled rate of invasive cervical cancer among women with SCCA cytology. Thus, articles that did not distinguish SCCA cytology from other types of smear abnormality such as adenocarcinoma were excluded. After combining data from six eligible studies retrieved from the search of standard bibliographic databases with the data from the present study, the pooled rate of underlying cervical cancer among women with SCCA cytology was 56% (942 patients, 95% CI 36 to 77). However, there was substantial heterogeneity (I^2=97.18%, $p<0.1$) among the studies included in the meta-analysis, which was a result of the wide variation in the rates of cervical cancer reported by the eligible studies (Figure 1)[3,6-10]. Subgroup analysis, a method for investigating heterogeneity that involved splitting all data into subgroups, for determining the impact of some differences across the included studies i.e., smear preparation techniques and background incidence of cervical cancer on the results of meta-analysis, could not be performed due to the limited number of studies included.

In the literatures, almost all invasive cancers found among women with smears indicating SCCA were cervical cancer[3,6-8]. Cancers with other origin sites were uncommon. In the study by Ruengkhachorn et al[10], out of 86 women with liquid-based smears suggesting SCCA, two patients (2.4%) were found to have vaginal SCCA and endometrial carcinoma. In the present study, all invasive lesions were cervical cancer.

The strength of the present study is that the previous studies evaluating the rates of cervical cancer among women with SCCA cytology were systematically searched and the results were pooled with those of the present study, by means of meta-analysis to be one overall measure of the available evidence.

Some limitations are worthy of note. First, the present study contained a relatively small sample size due to the rarity of SCCA smears. Second, some data were unavailable, such as previous history of cervical cancer screening and sexual behavior, which might influence the rate of underlying cervical lesions. Third, there were a limited number of women concurrently infected with HIV that underwent liquid-based cervical cytology and co-testing. Thus, the authors were unable to determine the impact of HIV infection, cervical smear preparation techniques, or the results of HR-HPV testing on the estimated risk of underlying lesions. Finally, there was no a central slide review in the present study.

In conclusion, approximately 50% of women with SCCA cytology in the present study were found to have cervical cancer. No significant clinical factors predicting underlying cervical cancer were noted.

After combining data from the previous studies and the present study, the pooled rate of underlying cervical cancer among women with SCCA cytology was 56%.

What is already known on this topic?

SCCA cytology is a rare cervical smear abnormality. Women with SCCA cytology carry an immense risk of having cervical cancer ranging from 28% to 80%.

What this study adds?

This study confirms the high frequency of cervical cancer among women with SCCA cervical cytology (52.2%). Through meta-analysis of the seven eligible studies (including the present study), the pooled rate of underlying cervical cancer among women with smears indicating SCCA was 56%.

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Conflicts of interest

The authors declare no conflict of interest.

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