
MINI-REVIEW

Histopathological Outcomes of Women with Abnormal Cervical Cytology: a Review of Literature in Thailand

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Abstract

Cervical cytology remains the principal screening method to detect pre-invasive and invasive cervical lesions. Management of abnormal cervical cytology depends on the risk of encountering a significant cervical lesion or high-grade cervical disease. These risks may vary in different areas across the country. Thus, determining the rate of significant cervical lesion associated with each type of abnormal cervical cytology in each area is of critical importance for designing area-specific management approach. This review was conducted to evaluate the rate of high-grade cervical disease among Thai women with abnormal cervical cytology. A relatively high incidence of underlying significant lesions including invasive disease was demonstrated even in those having only minimal smear abnormality. This baseline information is crucial and must be taken into consideration in management of women with abnormal cytological screening to achieve the goals of comprehensive cervical cancer control in Thailand.

Keywords: Cervical cancer - cytology - pathology - cancer control - Thailand

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Introduction

Cervical cancer remains the major health problem in Thailand and many other developing countries. This is mainly because of failure to initiate or sustain effective screening strategy. In recent population-based cancer registries, the highest incidence of cervical cancer in Thailand was noted in Chiang Mai with an average age-standardized incidence rate (ASR) of 28.9 per 100000, followed by Lampang (ASR, 22.4) and Bangkok (ASR, 20.9) (Moore et al., 2010).

Although high-risk Human Papillomavirus (HR-HPV) test and HPV genotyping have certain role in cervical cancer screening nowadays, these tests are not widely available in developing countries. Cervical cytology is still the principal screening method. Subsequent management of abnormal cervical cytology to detect underlying cervical lesions is also important. Generally, management of abnormal cervical cytology depends on the risk of encountering high-grade cervical disease. However, the risks of high-grade cervical disease encountered in abnormal cervical cytology may vary among different regions of the world and across the country. Therefore, information regarding the incidence of significant cervical disease from different areas or populations is crucial for designing and implementing area-specific management approach. This review was conducted to evaluate the incidence of high-grade cervical diseases among Thai

women with abnormal cervical cytology.

Methodological Approach

An electronic literature search was performed through PubMed, Scopus, Web of Science, and Thai database of health science journals (thailand.digitaljournals.org). A systematic search strategy was developed based on a preliminary scope of studies involving cervical histopathological outcomes among Thai women with abnormal cervical smears regardless of smear technique. However, only studies that applied the 2001 Bethesda System for reporting cervical cytology were included. Search terms were formulated based on an interpretation of the population/problem of interest, intervention and context (or PICO) framework (Cooke et al., 2012). Reference lists of eligible publications were reviewed to ascertain additional relevant papers. The authors may be contacted for more information if necessary. The last update searching was performed in April, 2014. The review results were reported according to type of smear abnormality.

Findings

Atypical squamous cells

One of the fundamental revisions of the 2001 Bethesda System for reporting cervical cytology was the elimination

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of atypical squamous cell of undetermined significance (ASCUS), favor reactive and ASCUS, not otherwise specified. All interpretations of ASC are qualified as “of undetermined significance” (ASC-US) or “cannot exclude high-grade squamous intraepithelial lesion” (ASC-H) (Solomon and Nayar, 2004).

Atypical squamous cells of undetermined significance

Criteria for interpretation of ASC-US include: 1) nuclei size of approximately two and one half to three times the area of the nucleus of a normal intermediate squamous cell; 2) slightly increased ratio of nuclear to cytoplasmic area; 3) minimal nuclear hyperchromasia and irregularity in chromatin distribution or nuclear shape; and 4) nuclear abnormality associated with dense orangeophilic cytoplasm, or the so-called “atypical parakeratosis” (Solomon and Nayar, 2004).

Seven previous studies from Thailand were reviewed (Table 1). Overall, the incidence of cervical intraepithelial neoplasia (CIN) 2-3/adenocarcinoma in situ (AIS) ranged from 8.0% to 18.5% (Kiatpongsan et al., 2006; Kantathavorn et al., 2008; Suntornlimsiri, 2010; Poomtavorn et al., 2011; Pothisuwan et al., 2011; Ekalaksananan et al., 2011; Kingnate et al., 2014;). These findings were in line with previous studies from North America (Levi et al., 2003; Boardman et al., 2006; Selvaggi, 2006; Sherman et al., 2006; Srodon et al., 2006; Feng and Husain, 2007; Safaeian et al., 2007; Siddiqui et al., 2008). Nevertheless, it should be noted that four studies from Thailand reported higher incidences of invasive cervical lesion than that reported among North American population: 1.7% to 7.9% (Kiatpongsan et al., 2006; Kantathavorn et al., 2008; Suntornlimsiri, 2010; Kingnate et al., 2014) vs less than 1.0% respectively (Levi et al., 2003; Boardman et al., 2006; Selvaggi, 2006; Sherman et al., 2006; Srodon et al., 2006; Feng and Husain, 2007; Safaeian et al., 2007; Siddiqui et al., 2008). As per the 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, the preferred method for managing women with ASC-US is a reflex HPV testing (Massad et al., 2013). Repeating cytology at 1-year interval is an acceptable alternative while colposcopy is not recommended as a primary investigation (Massad et al., 2013). In view of a high incidence of invasive lesion noted in some studies

in Thailand, an immediate colposcopy might be needed to detect the significant lesions especially in women who were expected to have poor compliance for a follow-up. In addition, the cost of colposcopy is much lower than that in the western countries.

Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion

Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) denotes cytological features with some, but not all, of the cytomorphologic criteria for high-grade squamous intraepithelial lesion (HSIL) (Solomon and Nayar, 2004). Immediate colposcopy is recommended for women with ASC-H cytology. Two studies on the histopathological outcomes of women with ASC-H conducted in Thailand were available for review (Table 1). In our previous report, the rate of significantly cervical lesion in women with smears revealing ASC-H was 75.0%, in which 9.3% were invasive cancer (Kietpeerakool et al., 2009). In the recent study by Kingnate et al (2014), incidence of CIN 2-3/AIS and invasive lesion was 10.5% and 2.6%, respectively. In the literature, almost all studies evaluating histopathologic results of ASC-H smears were reported from North America where the incidence of cervical cancer appears to be relatively low (Alli and Ali, 2003; Louro et al., 2003; Selvaggi, 2003; Liman et al., 2005; Barreth et al., 2006; Saad et al., 2006; Srodon et al., 2006; McHale et al., 2007). The rate of underlying high-grade cervical lesion varied widely from 10% to 80%, in which less than 3.5% were invasive lesion (Alli and Ali, 2003; Louro et al., 2003; Selvaggi, 2003; Liman et al., 2005; Barreth et al., 2006; Saad et al., 2006; Srodon et al., 2006; McHale et al., 2007).

Because of a lax criterion for interpreting ASC-H smear, poor interobserver agreement is anticipated which might be partly attributable for the wide variation of the rate of significant cervical lesion as have been noted in either Thai or North American settings (Quddus et al., 2001; Sherman et al., 2001). However, the notably high incidence of invasive lesion demonstrated (2.6%-9.3%) might indicate the necessity for aggressive management in Thai women with ASC-H cytology to make certain that occult invasive lesions could be detected and treated in a timely fashion.

Table 1. Histopathological Outcome in Thai Women with Atypical Squamous Cells on Cervical Smears

Authors	Smear type	Year	No. patients	Underlying histopathology		
				CIN 1 or less	CIN 2-3/AIS	Cancer
ASC-US						
Kiatpongsan et al		2006	90	76 (84.5)	11(12.2)	3 (3.3)
Kantathavorn et al		2008	208	179 (86.1)	24 (11.5)	5 (2.4)
Suntornlimsiri et al		2010	254	187 (73.6)	47 (18.5)	20 (7.9)
Poomtavorn et al		2011	266	229 (86.1)	37 (13.9)	0 (0)
Pothisuwan et al		2011	47	43 (91.5)	4 (8.5)	0 (0)
Ekalaksananan et al		2011	112	103 (92.0)	9 (8.0)	0 (0)
Kingnate et al		2014	779	677 (86.9)	89 (11.4)	13 (1.7)
ASC-H						
Kietpeerakool et al		2009	108	37 (34.1)	61 (56.5)	10 (9.3)
Kingnate et al		2014	152	132 (86.8)	16 (10.5)	4 (2.6)

ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia, AIS, adenocarcinoma in situ

Low-grade squamous intraepithelial lesion

In low-grade squamous intraepithelial lesion (LSIL) cytology, the cells are of the superficial or intermediate cell types which have enlarged nuclei that are 4-6 times the size of a normal intermediate cell nucleus. The nuclei are usually hyperchromatic, and multinucleation is common. However, in LSIL with marked HPV cytopathic changes, the nuclei are often only 2-3 times the size of a normal intermediate cell nucleus (Solomon and Nayar, 2004). In a region with a low incidence of cervical cancer, positive smear results for LSIL were associated with CIN2-3/AIS in approximately 12%-18% of women on initial colposcopy and with less than 1% of underlying invasive cancer (Massad et al., 2001; ALTS Group, 2003; Fairman et al., 2004; Chute et al., 2006). In Thailand, reported incidence of significant cervical pathology ranges from 11.2% to 32.2% (Table 2) (Khuakoonratt et al., 2008; Boonlikit, 2008; Kiatiyosnusorn et al., 2010; Ekalaksananan et al., 2011; Pothisuwan et al., 2011; Kingnate et al., 2014). The significant finding noted in some studies in Thailand is a relatively high incidence of underlying high-grade cervical lesion (11.2%-30.3%) and invasive lesion (1.3%-1.9%) (Khuakoonratt et al., 2008; Kiatiyosnusorn et al., 2010). Recommended management of LSIL cytology might be either colposcopy or cytological follow-up and varies between countries (Scheungraber et al., 2004). Nevertheless, immediate colposcopy might be appropriate in Thailand in which the patients' compliance is suboptimal (Rattanalappaiboon et al., 2014).

High-grade squamous intraepithelial lesion

High-grade squamous intraepithelial lesion (HSIL) cytology is acknowledged as a high-grade smear abnormality. The cytomorphologic features of squamous cells interpreting HSIL include an increased nuclear/cytoplasmic ratio, marked atypical nucleus, and irregular

nuclear border (Solomon and Nayar, 2004). Recommended management of women with HSIL cytology is either immediate colposcopy or immediate loop electrosurgical excision procedure (LEEP) after colposcopy, the so-called "see and treat" approach. Diagnostic cervical excision is advised if the colposcopic examination is inadequate, microinvasive carcinoma or low-grade lesion is identified on colposcopically-directed biopsy. Previous reported incidence of precancerous lesion and invasive cancer among population resided in low cervical cancer incidence areas ranges 60%-80% and 1-3%, respectively (Jones and Davey, 2000; Massad et al., 2001; Szurkus and Harrison, 2003; Berdichevsky et al., 2004; Boman et al., 2004; Numnum et al., 2005; Chute et al., 2006; Sadan et al., 2007). In Thailand, although incidence of CIN2-3 and AIS in women with HSIL smears (62% to 74%) paralleled those reports of other populations, the incidences of underlying invasive disease were remarkably higher ranging from 7.9% to 25.8% (Kantathavorn et al., 2006; Boonlikit, 2008; Aue-Aungkul et al., 2011; Sripipattanakul, 2011; Ingkapairoj et al., 2012; Kingnate, et al., 2014) (Table 2). Therefore, intensive evaluation of Thai women with HSIL smears is mandatory in order to exclude occult invasive lesion.

Squamous cell carcinoma cytology

Squamous cell carcinoma (SCCA) cytology is sparse. In general, SCCA cytology could be subdivided into 2 categories including keratinizing and non-keratinizing types. In nonkeratinizing type, cells display most of the cytological characteristics of HSIL. Tumor diathesis is frequently present. In contrast, the pathognomonic feature of smear suggesting keratinizing squamous cell carcinoma is a marked variation in cellular size and shape. A tumor diathesis is usually less than that observed in non-keratinizing type (Solomon and Nayar, 2004).

Table 2. Histopathological Outcome in Thai Women with Cervical Smears Revealing LSIL, HSIL and SCCA

Authors	Smear type	Year	No. patients	Underlying histopathology		
				CIN 1 or less	CIN 2-3/AIS	Cancer
LSIL						
Khuakoonrat et al		2008	226	189 (83.6)	34 (15.0)	3 (1.3)
Boonlikit et al		2008	250	222 (88.8)	28 (11.2)	0 (0)
Kiatiyosnusorn et al		2010	208	141 (67.8)	63 (30.3)	4 (1.9)
Ekalaksananan et al		2011	78	68 (87.2)	10 (12.8)	0 (0)
Pothisuwan		2011	51	41 (80.4)	10 (19.6)	0 (0)
Kingnate et al		2014	395	315 (79.8)	76 (19.2)	4 (1.0)
HSIL						
Kantathavorn et al		2006	681	38 (5.6)	502 (73.7)	141 (20.7)
Boonlikit et al		2008	152	37 (24.3)	103 (67.8)	12 (7.9)
Sripipattanakul		2011	179	33 (18.4)	114 (63.7)	32 (17.9)
Aue-aungkul et al		2011	124	14 (11.3)	78 (62.9)	32 (25.8)
Ingkapairoj et al		2012	302	78 (25.8)	196 (64.9)	28 (9.3)
Kingnate et al		2014	143	36 (25.2)	89 (62.2)	18 (12.6)
SCCA						
Charoenkwan et al		2006	48	1 (2.1)	31 (64.6)	16 (33.3)
Aue-aungkul et al		2011	9	0 (0)	4 (44.4)	5 (55.6)
Ruengkachorn et al		2012	86	2 (2.3)	13 (15.1)	71 (82.6)
Kingnate et al		2014	31	2 (6.5)	5 (16.1)	24 (77.4)

*LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCCA, squamous cell carcinoma; CIN, cervical intraepithelial neoplasia, AIS, adenocarcinoma in situ

Data regarding cervical pathology among women with SCCA cytology are limited due to the rarity of this smear abnormality. Two studies conducted in US population demonstrated approximately 15%-24% the risk of harboring invasive lesion in women with SCCA cytology (Jones and Davey, 2000; Massad et al., 2001). These rates were much lower than those reported in the studies from Thailand. The study conducted in Chiang Mai reported that the incidence of significant cervical lesion in SCCA cytology was 98%, in which 33.3% were invasive disease (Charoenkwan et al., 2006). Another study by Aue-aungkul et al (2011), in evaluating the clinical feasibility of the see and treat approach in managing Thai women with abnormal cervical cytology, from the same hospital reported that approximately 55.6% of women with SCCA cytology had invasive cervical lesions. An extraordinarily high incidence of underlying invasive lesion in women with SCCA cytology was concordantly found in recent reports from the other areas of Thailand by Ruengkachorn et al (2012) and Kingnate et al (2014): 82.5% and 77.4% respectively. Thus, a high likelihood of harboring invasive disease in Thai women with SCCA smears should be kept in mind while taking care of women with SCCA cytology.

Atypical glandular cells

Screening for glandular disease of cervix remains among the major issues in gynecologic cytopathology. The 2001 Bethesda System has revised the reporting cervical smear interpreting glandular abnormality (Solomon and Nayar, 2004). This was in order to improve communication between laboratories and clinicians, indicate understanding of features of glandular neoplasia in cervical smear thereby result in appropriate approach for the patients.

A challenge in evaluating women with AGC bases on a wide variety of potential sites origin ranging from endocervix, endometrium, fallopian tube, ovary, and even of very rarely from extragenital sites. Per the 2001 Bethesda System, atypical glandular cells (AGC) is categorized according to the sites of origin (endocervical or endometrial) whenever feasible; otherwise, the generic "AGC" is used. Atypical endocervical cells may be further qualified as "favor neoplasia", if not so, "not otherwise specified (NOS) may be stated. Atypical endometrial cells are not recommended to be further qualified because of unreliable subcategorizing this category (Solomon and Nayar, 2004).

Initial management in women with AGC cytology consists of colposcopy and endocervical sampling. Additional endometrial sampling is recommended in women 35 years of age or older, and in women at risk of endometrial neoplasia. In the literature, the incidence of significant lesion in women with AGC-NOS varies from 5% to 33% (Haidopoulos et al., 2005; DeSimone et al., 2006; Behtash et al., 2007; Westin et al., 2008; Adhya et al., 2009; Schnatz et al., 2009; Zhao et al., 2009) as compared with 41%-70% in women with AGC-FN smears (Haidopoulos et al., 2005; DeSimone et al., 2006; Westin et al., 2008; Adhya et al., 2009; Schnatz et al., 2009). Extragenital malignant lesions were found in less than

1% of women with AGC cytology (Zhao et al., 2009).

Four studies on the underlying lesions in women with AGC cytology conducted in Thailand were identified. Firstly, Sawangsang et al (2011) from Chiang Mai University Hospital reported that approximately 15% of women with AGC-NOS smears had significant lesions (CIN2-3, AIS, atypical endometrial hyperplasia, cancer), in which 2.2% were invasive lesions and all were cervical cancer. Of women with AGC-FN cytology, approximately 41.2% had significant lesions, in which, respectively, 17.6% and 5.9% were endometrial adenocarcinoma and cervical cancer.

Additional three studies were conducted in Bangkok. Lojindarat et al (2012) reported 32.4% significant lesions in women with smear interpreting AGC, in which 18.3% were invasive lesion. Diagnoses of underlying significant lesion after AGC-FN were significantly more likely than those with AGC-NOS smears (53.8% vs 20.0%). Chatchotikawong et al (2012) reported that the likelihood of cancer precursor and malignant histologic results in the AGC-NOS group was 31.7% and 23.7%, respectively, as compared with 65.4% and 55.1% of women in the AGC-FN group. An interesting finding in this study was a relatively high incidence of extragenital malignant lesions (3.8% of AGC-NOS and 5.1% of AGC-FN smears) (Chatchotikawong et al., 2012). Recently, Kingnate et al (2014) observed that approximately 10.4% and 4.5% of women with AGC-NOS smears had CIN 2-3/AIS and invasive lesion, respectively. For women with AGC-FN, the incidence of significant lesion was 15% in which 5% were invasive lesion.

Conclusion

This review documents a relatively high rate of significant lesions particularly invasive disease among Thai women with abnormal cervical cytology screening even in those having only minimal smear abnormality. This baseline information must be taken into consideration in management of women with abnormal cytological screening to achieve the goals of comprehensive cervical cancer control in Thailand.

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