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Retrospective analysis of cervical cancer and precancerous lesions in patients with atypical squamous cells of undetermined significance in China

Yan-Ying Wang, MD[a], Ling-Hua Kong, MD[b], Yang Liu, MD[b], Shu Wang, MD[b,*], Qing-Bo Fan, MD[b,*], Lan Zhu, MD[b], Jing-He Lang, MD[b]

Abstract

Atypical squamous cells of undetermined significance (ASCUS) are the most common cytological abnormality of all smear test. No study has demonstrated the prevalence of cervical cancer or its precursor in Chinese patients with ASCUS. This study aims to investigate the prevalence of cervical intraepithelial neoplasia 1 or worse (CIN1+) and CIN3 or worse (CIN3+) in patients with ASCUS in China to provide insight into appropriate management for Chinese health care.

In a retrospective cross-sectional study, patients who underwent liquid-based thin layer cytology and human papillomavirus (HPV) co-testing at the Peking Union Medical College Hospital between January 2014 and January 2017, and had ASCUS results on liquid-based thin layer cytology test and underwent follow-up and colposcopic biopsy were included. Age, HPV DNA test, and pathological outcomes were assessed.

One hundred forty-four patients with ASCUS and positive HPV test results were included. In the 3-year follow-up, 23 (16.0%) patients had CIN1, 28 (19.4%) had CIN2, and 17 (11.8%) had CIN3 or carcinoma in situ. The risk of CIN3+ was significantly higher in those older than 60 years (42.8%, $P = .005$), whereas the CIN1+ prevalence displayed no significant difference between age groups. Both hybrid Capture II (HC II) value and cytopathological description of HPV infection showed no statistically significant correlation with CIN1+ or CIN3+.

Patients with HPV-positive ASCUS who were older than 60 years had a significantly higher risk of CIN3+, and clinicians should pay more attention to them. Both HC II value and cytopathological description of HPV infection showed no significant correlation with CIN1+ or CIN3+.

Abbreviations: ASCUS = atypical squamous cells of undetermined significance, CIN1+ = cervical intraepithelial neoplasia 1 or worse, CIN2+ = cervical intraepithelial neoplasia 2 or worse, CIN3+ = cervical intraepithelial neoplasia 3 or worse, CIS = carcinoma in situ, HC II = hybrid capture II, HPV = human papillomavirus, HSIL = high squamous intraepithelial lesion, LSIL = low squamous intraepithelial lesion, ROC = receiver operating characteristic, TCT = Thinprep cytologic test.

Keywords: atypical squamous cells of undetermined significance, cervical cancer, cervical intraepithelial neoplasia, human papillomavirus, Thinprep cytologic test, screening

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Y-YW, and L-HK contributed equally to this study.

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[a] Peking Union Medical College, [b] Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

[*] Correspondence: Shu Wang, Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Beijing 100730, China (e-mail: wangshu219@hotmail.com); Qing-Bo Fan, Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Beijing 100730, China (e-mail: qbfan@sohu.com).

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1. Introduction

Worldwide, cervical cancer is the fourth most frequent cancer in women with an estimated number of 570,000 new cases in 2018. Of the >311,000 estimated deaths from cervical cancer every year, >85% occur in less developed regions.[1] There is still a heavy burden of cervical cancer in China, with an estimated number of 102,000 new cases in 2014.[2] Fortunately, both morbidity and mortality of cervical cancer could be decreased with the optimal strategy for screening and management of precancerous lesions.

Cytologic study of cervical smear sample is regarded as the most cost-effective method of detecting precursor lesions of cervical cancer. According to the Bethesda System for Reporting Cervical Cytology, there are 2 forms of squamous intraepithelial lesion: low squamous intraepithelial lesion (LSIL) and high squamous intraepithelial lesion (HSIL) grade, and 2 subcategories of atypical squamous cell (ASC): atypical squamous cells of undetermined significance (ASCUS) and ASCs, cannot exclude high-grade squamous intraepithelial lesion.[3] ASC is used to describe dubious and abnormal histology in squamous cells, which usually indicates inflammation, reactive and repair changes, or a precancerous lesion resulted from persistent human papillomavirus (HPV) infection.[4] ASCUS is defined as the ASC result which resembles but does not meet LSIL criteria.[3]

ASCUS is the most common cytological abnormality ranging from 1.6% to 9% of all smear test results, whereas the least reproducible result.[5,6] The optimal ASCUS triage should be able to identify those patients who require treatment and avoid unnecessary procedures. There is, however, controversy regarding the most appropriate procedure to prevent ASCUS from evolving into more advanced cervical lesions.[7]

In 2012, the American Society for Colposcopy and Cervical Pathology published the updated consensus guidelines for managing abnormal cervical cancer screening tests and precancerous precursors.[8] The recommended management for women with ASCUS is either repeat cytology by the first year or to perform HPV testing. Negative results for HPV practically guarantee benign ASCUS and follow-up with co-testing by the third year is suggested.[8,9] By contrast, colposcopy is indicated for all women with HPV-positive ASCUS according to the guidelines, because the 5-year cumulative risk for cervical intraepithelial neoplasia (CIN) 2 or worse (CIN2+) among women testing HPV-positive ASCUS was close to that of women with LSIL.[10] However, no study have demonstrated the prevalence of cervical cancer or its precursor in Chinese patients with ASCUS. In addition, the more ideal outcome to be chosen could be CIN3+, as low and moderate CINs often regress and are less reproducible. Although in a clinical setting, CIN2+ is of great interest as it is the threshold for treatment.[11]

In this study, we aimed to investigate the prevalence of CIN1+ and CIN3+ in patients with HPV-positive ASCUS to provide insight into appropriate management for Chinese health care.

2. Methods

In our retrospective cross-sectional study, patients who underwent liquid-based thin layer cytology and HPV co-testing at the Peking Union Medical College Hospital between January 2014 and January 2017, and had ASCUS results on Thinprep cytologic test (TCT) as well as underwent follow-up and colposcopic biopsy were included. Women whose HPV DNA test result were positive but did not complete the corresponding biopsy were excluded. Those who had undergone hysterectomy or were pregnant at the time of cervical cytology were also excluded.

The study was approved by the Ethics Committee of our hospital (S-K671) and was conducted in accordance with the Declaration of Helsinki as revised in 2013. Informed consents were obtained from the patients for the purpose of publication. Clinicopathologic variables of the patients including age at the time of the combining test, the results of cervical cytology, HPV DNA test, and punch biopsy were obtained from the review of the electronic medical record system.

Cytology was performed by TCT from ThinPrep Papanicolaou tests (Cytyc Corporation, Marlborough, MA). Cytological diagnosis of ASCUS was classified using the 2001 Bethesda System Nomenclature. The detection of high-risk HPV infection was conducted either by hybrid capture (HC) II HPV test (Digene, Gaithersburg, MD) or by HPV DNA genotyping (Digene) according to the physician's preference. For the former method, specimens tested with relative light units/cutoff value ratios >1.0 were considered positive for 1 or more high-risk HPV genotypes including the following 13 genotypes: HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The latter method identified 17 HPV types including 15 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 82). Genomic DNA extraction, amplification, labeling, hybridization, and analysis were performed according to the manufacturer's instructions.

Data were analyzed via SPSS for version 24.0 (IBM, Armonk, NY). Data were compared by Pearson χ^2 or Fisher exact tests as appropriate. Receiver operating characteristic (ROC) curves were adopted to analyze continuous variables. $P < .05$ was considered to be statistically significant. When comparing 4 age groups with the same control group separately, the Bonferroni method was used to correct $\alpha = 0.05$ to $\alpha' = 0.0125$, in which condition $P < .0125$ was considered to be statistically significant.

3. Results

A total of 420 patients with ASCUS were included. Among them, 144 (34.3%) with positive results of HPV DNA test were identified and formed the study base of this analysis. The median age of the patients with HPV-positive ASCUS was 44 years. Among them, no one was aged <20 years, 9 (6.2%) were aged 20 to 29 years, 44 (30.6%) 30 to 39 years, 50 (34.7%) 40 to 49 years, 27 (18.8%) 50 to 59 years, and 14 (9.7%) ≥60 years (Table 1).

When colposcopic biopsy results were within 3 years of TCT and HPV co-testing, among these 144 women, 23 (16.0%) had CIN1, 28 (19.4%) had CIN2, and 17 (11.8%) had CIN3 or carcinoma in situ (CIS). No case of invasive cervical cancer was found. CIN1+ patients accounted for 47.2% (68/144) of the total, and CIN3+ took up 11.8% (17/144). In the 5 age groups, patients in 20- to 29 and ≥60-year groups had relatively high rates of CIN1+, which were 66.7% and 64.3%, respectively. The 50- to 59-year group showed the lowest rate of 37%, but no statistical significance was found between the 5 groups ($P = .32$). However, the percentage of CIN3+ of the 5 groups displayed a significant difference ($P = .018$) (Table 1). Further comparing other groups to 30 to 39 years (6.8%) revealed that the percentage of CIN3+ significantly increased in patients 60 years or older (42.8%, $P = .005$), whereas differences were not significant in other groups [50–59 years (7.4%, $P > .99$); 40–49 years (10%, $P = .86$); 20–29 years (11.1%, $P > .99$)].

Table 1

The distribution of histologic outcomes according to age groups in patients with atypical squamous cells of undetermined significance and positive human papillomavirus test (a 3-year follow-up)[*].

	Total	20–29 y	30–39 y	40–49 y	50–59 y	≥60 y	P[†]
No.	144	9	44	50	27	14	
Age [Median (IQR; range)]	[44 (35, 51.75; 25–77)]	[27 (25, 28; 25–29)]	[35 (33, 37; 31–39)]	[45.5 (42, 48; 40–49)]	[54 (52, 57; 50–59)]	[62 (61, 67.25; 60–77)]	
CIN1+	68 (47.2%)	6 (66.7%)	22 (50%)	21 (42%)	10 (37%)	9 (64.3%)	.32
CIN3+	17 (11.8)	1 (11.1%)	3 (6.8%)	5 (10%)	2 (7.4%)	6 (42.8%)	.018

CIN1+ = cervical intraepithelial neoplasia grade 1 or worse, CIN3+ = cervical intraepithelial neoplasia grade 3 or worse, IQR = interquartile range.

[*] Values are given as number (percentage), unless indicated otherwise.

[†] Data were compared by Pearson χ^2 or Fisher exact tests as appropriate, and $P < .05$ was considered to be statistically significant.

Shortening the follow-up time to only 1 year, the histologic outcomes showed that 9 (6.2%) patients had CIN1, 17(11.8%) had CIN2, and 7 (4.9%) had CIN3 or CIS. No case of invasive cervical cancer was found. CIN1+ patients accounted for 22.9% (33/144) of the total, and CIN3+ took up 4.9% (7/144). In the 5 age groups, the percentage of CIN1+ varied from 0.0% (≥60 years) to 34.1% (30–39 years), with no statistical significance ($P = .32$). The comparison between the groups also showed no significant difference in the percentage of CIN3+, changing from 0.0% (20–29 years, ≥60 years) to 9.1% (30–39 years) ($P = .47$) (Table 2).

The 144 patients were divided into 2 groups according to whether there was a cytopathological description of HPV infection in their TCT reports or not. Sixty-five of them were positive for cytopathological HPV infection and 79 negative. The Chi-square test demonstrated that there was no significant difference in the prevalence of CIN1+ or CIN3+ within 3 years between these 2 microscopic HPV groups. The *P* values of the Chi-square test were .37 (CIN1+ group) and .17 (CIN3+ group) separately (Table 3).

Among the 144 patients with ASCUS and positive HPV results, 114 had their HPV DNA test by HC II. There were 58 patients with CIN1+ biopsy results and the median HC II value was 161.7. Sixteen patients had CIN3+ outcomes, with a median HC II value of 60.0. Fifty-six patients were CIN− and their median HC II value was 123.0. ROC analysis indicated no statistical significance neither between CIN1+ and CIN− ($P = .54$) nor between CIN3+ and CIN− ($P = .20$) (Table 4).

4. Discussion

ASCUS is the most common cytological abnormality and its morbidity is increasing in young women.[12] The cytologic conditions initially found in the ASCUS group were not sufficient to diagnose the level of the risk, but enough to indicate that the patients should not be treated as a normal group.[7] Colposcopy with directed biopsy is a criterion standard strategy for CIN detection. However, biopsy results of patients with ASCUS cytology revealed only 1.1% CIN2, 3.8% CIN3, and 0.9% cervical squamous cell carcinoma at biopsy, leading to many unnecessary colposcopy procedures.[13] In addition, not all hospitals in China have a standard colposcopy service with well-trained physicians. There is a long waiting list for colposcopy in our institute.

The HPV triage is a high sensitivity test and is considered as the most cost-effective strategy according to several previous studies.[14] The present finding revealed that the frequency of HPV was 34.3% among patients with ASCUS in China, which is lower than that which was previously reported in the literature, possibly varying with the technique used and the population studied.[15] Two Brazilian studies demonstrated the prevalence of HPV in women with ASCUS was 64.39% and 60.0%, respectively.[4,7] The highly impactful ALTS study reported a rate of HPV slightly above 50% for ASCUS patients.[4] However, research from Taiwan displayed that high-risk HPV genotypes were present in 36.2% of 105 women with ASCUS, which is quite similar to our study. Another study from Thailand observed a high-risk HPV positivity of 40% in women with ASCUS.[16] Approximately 65% of the women with ASCUS cytology in the present study had a negative result for HPV test and could avoid an unnecessary colposcopy.

In our study, cervical biopsy results of women with HPV-positive ASCUS (n = 144) revealed that 47.2% (n = 68) of the patients had CIN1+, 31.2% had CIN2+, and 11.8% (n = 17) had CIN3+ within a 3-year follow-up. In a 1-year follow-up, this

Table 2

The distribution of histologic outcomes according to age groups in patients with atypical squamous cells of undetermined significance and positive human papillomavirus test (a 1-year follow-up)[*].

	Total	20–29 y	30–39 y	40–49 y	50–59 y	≥60 y	P[†]
No.	144	9	44	50	27	14	
Age [Median (IQR; range)]	[44 (35, 51.75; 25–77)]	[27 (25, 28; 25–29)]	[35 (33, 37; 31–39)]	[45.5 (42, 48; 40–49)]	[54 (52, 57; 50–59)]	[62 (61, 67.25; 60–77)]	
CIN1+	33 (22.9%)	2 (22.2%)	15 (34.1%)	10 (20%)	6 (22.2%)	0 (0.0%)	.083
CIN3+	7 (4.9%)	0 (0.0%)	4 (9.1%)	1 (2.0%)	2 (7.4%)	0 (0.0%)	.47

CIN = cervical intraepithelial neoplasia, IQR = interquartile range.

[*] Values are given as number (percentage), unless indicated otherwise.

[†] Data were compared by Pearson χ^2 or Fisher exact tests as appropriate, and $P < .05$ was considered to be statistically significant.

Table 3

Effects of microscopic human papillomavirus on histologic outcomes in patients with atypical squamous cells of undetermined significance and positive human papillomavirus test (a 3-year follow-up)[*].

			Cytopathologically positive of HPV		
		No.	Yes	No	P[†]
Total		144	65	79	
CIN1+ group	CIN1+	68	28 (43.1%)	40 (50.6%)	.37
	CIN−	76	37 (56.9%)	39 (49.4%)	
CIN3+ group	CIN3+	17	5 (7.7%)	12 (15.2%)	.17
	CIN− + CIN1-2	127	60 (92.3%)	67 (84.8%)	

CIN = no cervical intraepithelial neoplasia or cervical cancer, HPV = human papillomavirus, microscopic HPV = whether there was cytopathological description of HPV infection in Thinprep cytologic test (TCT) reports or not.

[*] Values are given as number (percentage), unless indicated otherwise.

[†] Data were compared by Pearson's $\chi 2$, and $P < .05$ was considered to be statistically significant.

study showed 22.9% CIN1+, 16.7% CIN2+, and 4.9% CIN3+. The prevalence of CIN was higher in our study than in previous studies. In Thailand, Tantitamit found 11.8% CIN2+ in women with HPV-positive ASCUS, whereas another research described a prevalence of 14.3%.[14,17] Katki et al[10] reported a 5-year risk of CIN3+ of 6.8% among women having HPV-positive/ASCUS test results. The risk stratification concept involving "equal management of equal risks" by Castle et al stated that it is safe to return the patient to the regular screening if the 5-year risk of CIN3+ is <2%. If the risk is between 2% and 10%, follow-up by the first year is recommended and a risk >10% referral colposcopy is needed.[18] As in our study, the 3-year risk of CIN3+ had already been >10%. Thus, referral colposcopy is necessary for Chinese women having HPV-positive/ASCUS test results.

A previous study on women aged 23 to 60 years with a baseline ASCUS or LSIL cytology indicated that the 3.5-year cumulative risk of developing CIN2+ was the greatest among women aged between 30 and 39 years.[11] Our study revealed a significantly higher prevalence of CIN3+ in ≥60-year group (42.8%) comparing to 30- to 39-year group (6.8%) in the 3-year follow-up, whereas no significant difference was found when comparing other groups to the 30- to 39-year group. Therefore, age could be a factor that influences the prevalence of CIN in women with ASCUS. In the 3-year follow-up, our study did not find any difference in CIN1+ between the age groups. In the 1-year follow-up, the rate of CIN1+ and CIN3+ did not show any significant difference between the age groups. Except for pathological outcomes, age also had an impact on the false negative rate of HPV test in patients with ASCUS. As the age advanced, the specificity of HPV DNA test increased, whereas the sensitivity decreased. The false negative rate of patients >60 years with ASCUS was as high as 33.3%, compared to 0% in their youngest counterpart.[19] A study from the Norwegian Cervical Cancer Screening Program reported that the risk for CIN2+ in HPV-negative women with persistent ASCUS/LSIL was >2% and that returning these women to the normal screening was potentially unsafe.[20] Further investigation is needed in the Chinese population concerning whether HPV-negative ASCUS findings should be treated as negative cytology results, especially for women older than 60 years.

HPV infection promotes a series of cytoplasmic and nuclear alterations observable by cytology. Koilocytosis and dyskeratosis are pathognomonic of HPV infection.[21] In addition, bi/multinucleation and hyperkeratosis can also indicate but not define HPV infection.[5] Previous literature diverges regarding an association of these cytopathological HPV infection findings with HSIL, but studies have demonstrated a significant association with LSIL and cytopathic HPV effects.[22,23] In our study, comparing cytopathological HPV infection with CIN1+ and CIN3+ histopathological results did not yield statistically significant correlations.

Several large randomized controlled studies and longitudinal cohort studies have demonstrated that HPV negativity is protective against the development of pre-cancer.[11] The relationship between HPV and carcinogenesis has been well established, depending basically on the viral genotype (high- or low-risk HPV), viral load, viral persistence, and integration with the host cell.[24] The high incidence of HPV observed among patients with ASCUS could be at least partly explained by the fact that most cases of ASCUS progressed to LSIL or HSIL. The cytologic effect that allows the classification of the lesion as ASCUS is possibly linked to the viral load and the resulting physiologic cellular effects.[7] The viral load could be reflected by the HC II value. This study explored the effects of the HC II value

Table 4

Effects of hybrid capture II value on histologic outcomes in patients with atypical squamous cells of undetermined significance and positive human papillomavirus test (a 3-year follow-up).

		HC II (RLU/CO)		
		No.	Value [median (IQR; range)]	P[*]
CIN1+ group	CIN1+	58	[161.7 (28.3,524.1; 2.0–22244.1]	.54
	CIN−	56	[123.0 (12.3,538.3; 1.1–3631.4)]	
CIN3+ group	CIN3+	16	[60.0 (12.8,227.1; 2.0–2218.3)]	.20
	CIN−	56	[123.0 (12.3, 538.3; 1.1–3631.4)]	

CIN = cervical intraepithelial neoplasia, HC II = hybrid capture II, RLU/CO = relatively light units/cutoff.

[*] Receiver operating characteristic curves were used to analyze continuous variables, and $P < .05$ was considered to be statistically significant.

on histologic outcomes among patients with HPV-positive ASCUS, but no significant correlation was found in both CIN1+ and CIN3+.

Its population size and its novelty comprise the strengths of this study. At the same time, there are also several limitations in this study. First, the data were evaluated from files in one laboratory (selection bias). Second, this is a retrospective cross-sectional study in a single institution which cannot represent the entire population in China. Further investigations with a better study design are needed to prove the findings in our study. Lastly, 2 different HPV DNA tests were used for detecting high-risk HPV infection. Nevertheless, the 2 methods were reported to have similar diagnostic performances.

In conclusion, our study found age as an indicator for identifying higher-risk ones among patients with HPV-positive ASCUS. Patients with HPV-positive ASCUS who were older than 60 years had a significantly higher risk of CIN3+ and clinicians should pay more attention to them. We also clarified 2 clinical misunderstandings. Both HC II value and cytopathological description of HPV infection showed no significant correlation with CIN1+ or CIN3+. The results will help to guide the physicians in counseling and managing the women with HPV-positive ASCUS in the prevention of cervical cancer.

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Author contributions

W-YY: study design, literature search, data acquisition, statistical analysis, manuscript preparation, and manuscript editing. K-LH: study design, statistical analysis, manuscript preparation, and manuscript editing. LY: literature search, data acquisition, manuscript preparation. WS: study design, definition of intellectual content, literature search, statistical analysis, manuscript preparation, and manuscript review. F-QB: study design, definition of intellectual content, statistical analysis, manuscript review. ZL: definition of intellectual content, manuscript review. L-JH: definition of intellectual content, manuscript review.

Shu Wang orcid: 0000-0001-5447-0946.

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