

*Original Research Article*

# Prevalence of cervical intraepithelial neoplasia (CIN) among women with ASC-US cytology in Saudi Population

Abdulrahim Gari<sup>1,2\*</sup> and Nouf Ali Behzad<sup>2,3</sup>

Abstract

<sup>1</sup>Assistant Professor, Department of Obstetrics and Gynecology, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

<sup>2</sup>King Faisal Specialist Hospital and Research Center, Dept. of Obstetrics and Gynecology, Jeddah, Saudi Arabia

<sup>3</sup>Salmaniyah Medical Complex- Dept. of Obstetrics and Gynecology, Kingdom of Bahrain

\*Corresponding Author's E-mail: [gari505@yahoo.ca](mailto:gari505@yahoo.ca)  
Mobile: +966542671111

A typical squamous cells of undetermined significance (ASC-US) carry the lowest risk of invasive cervical cancer among the other abnormal cervical cytology. Early detection of premalignant conditions following abnormal Pap smear results helps significantly in the prevention and early management of cervical dysplasia; hence, in the reduction in mortality and morbidity of cervical cancer. To determine the prevalence of premalignant pathology, cervical intraepithelial neoplasia (CIN), associated with ASC-US Pap smear results in Saudi Arabian women. The results would help to establish the importance of following ASCUS Pap results with HPV testing. It would also demonstrate the role of ASCUS cytology in predicting cervical intraepithelial neoplasia 1, 2 and 3. A retrospective cross-sectional study was carried to evaluate all ASC-US pap smears, and this was followed by colposcopic-directed biopsy in the period between January 2013 and December 2015. Histopathologic findings of CIN1, 2 and 3 after single or repeated ASC-US results were obtained and included in the study. The majority of ASC-US cases were in premenopausal women, particularly those below the age of 40 years. It was found that 3.9% of colposcopy-directed biopsies results were positive for CIN1 and 4.6% showed koilocytosis. ASC-US, particularly CIN1, carry a low risk of cervical dysplasia and cancer.

**Keywords:** Abnormal PAP smear, ASC US, Atypical squamous cells of undetermined significance, Cervical dysplasia, Colposcopy

## INTRODUCTION

Cervical cancer is common among women worldwide with its incidence rate related to screening and HPV vaccination (Walboomers et al., 1999; Nobbenhuis et al., 1999). Since the introduction of Papanicolaou (Pap) test, it has been used in cervical cancer screening program to detect premalignant lesions and early stages of cervical cancer (Benedet et al., 1992). Cervical intraepithelial neoplasia (CIN) is a premalignant condition which refers to squamous abnormality. The risk of invasive cancer with ASC-US Pap smear is low because one to two-thirds

of cases are not associated with high-risk HPV infection (ASCUS-LSIL triage study (ALTS) group, 2003; Katki et al., 2013). This study investigates the prevalence of premalignant pathology associated with ASCUS Pap smear in women. The results would help to establish whether it is important to follow up ASC-US Pap results with HPV testing and would demonstrate the significance of ASC-US cytology in predicting cervical intraepithelial neoplasia 1, 2 and 3.

**Table 1.** Age distribution of women with ASCUS.

	Mean	95% Confidence Interval	
		Lower	Upper
<b>Age mean(SD) .</b>	43.5 (12.5)	42.45	44.48
40 Yrs. or less n(%)	260(46.9%)	43.90%	51.80%
> 40 to 60 Yrs. n(%)	223(41.1%)	37.10%	45.20%
> 60 Yrs. n(%)	60(11%)	8.70%	13.60%

**Table 2.** Age distribution of women with ASC-US pap smear

		agegrp							
		Frequency	Percent	Valid Percent	Cumulative Percent	Bootstrap for Percent <sup>a</sup>			
						Bias	Std. Error	Lower	Upper
Valid	40 Yrs. or less	260	47.9	47.9	47.9	-.1	2.2	43.9	51.8
	>40 to 60 Yrs.	223	41.1	41.1	89.0	.0	2.1	37.1	45.2
	>60 Yrs.	60	11.0	11.0	100.0	.1	1.3	8.7	13.6
	Total	543	100.0	100.0		.0	.0		

a. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples

**Table 3.** Distribution of second PAP smear results for all cases .N=543.

	Frequency	Percentage	95% C.I percentage.	
			Lower	Upper
ASCUS	80	14.7	11.6	17.7
LSIL	13	2.5	1.3	3.7
Not done	294	54.1	50.2	58.6
Negative	156	28.7	25.4	32.2
Total	543	100		

## METHODOLOGY

A cross-sectional retrospective survey of ASC-US-reported cervical smears was conducted between January 2013 and December 2015 at the Obstetrics and Gynecology department at King Faisal Specialist Hospital and research center, Jeddah. Liquid-based cytology samples with ASC-US Pap smear results were retrieved from department of pathology at King Faisal Specialist Hospital and research Center, Jeddah. Colposcopy-directed biopsy results following single or repeated ASC-US Pap smears were traced through patients' electronic records.

### Inclusion criteria

All married Saudi women, aged 20 years and above, with ASC-US Pap smear collected in Ob-Gyn clinic, were included in the study.

### Exclusion criteria

Pregnant women were excluded from the study. All the

the collected data were statistically analyzed using SPSS program.

## RESULTS

A total of 543 women with ASC-US Pap smear results were included in the study group in the period between January 2013 and December 2015. The majority of the women in the study group were less than 40 years old (46.9%); however, 41.1% were aged 40-60 years while only 11% were older than 60 years old. The mean age of the study group was 43.5 years (Table 1, 2).

Only 249 women from the study population had repeated a PAP test within six months to one year after the first ASC-US Pap smear. Out of the 249 women who repeated the test, 80 (14.7%) still obtained an ASCUS result; that is, a second ASCUS Pap result (C.I.11.6-17.7). Only 2.5% had LSIL Pap result and 156 (28.7%) were negative (normal) results (C.I. 25.4-32.2) (Table 3). One patient showed atypical glandular cells (AGC - NOS) and was excluded from the study.

Colposcopic assessment was done for only 86 women who had either a single ASC-US result or two consecutive ASC-US results. Among those who had

**Table 4.** Distribution of the Colposcopy Outcomes for the 543 cases.

	Count	Percentage	95% C.I percentage.	
			Lower	Upper
CIN1	21	3.9	2.5	5.3
Koilocytosis present	25	4.6	2.9	6.4
LSIL	13	2.4	1.3	3.7
Not done	457	84.2	81.2	87.2
Normal result.	27	5	3.3	6.8
Total	543			

1 case with AGCNOS excluded.

**Table 5.** Colposcopy results in the study period

		colpos * Yrs Crosstabulation				
		Yrs			Total	
		2013	2014	2015		
colpos	CIN1	Count	6	8	7	21
		% within Yrs	3.0%	5.0%	3.9%	3.9%
		% of Total	1.1%	1.5%	1.3%	3.9%
		Adjusted Residual	-.9-	.9	.0	
	KOILO	Count	7	10	8	25
		% within Yrs	3.4%	6.2%	4.5%	4.6%
		% of Total	1.3%	1.8%	1.5%	4.6%
		Adjusted Residual	-1.0-	1.2	-.1-	
	LSIL	Count	2	2	9	13
		% within Yrs	1.0%	1.2%	5.0%	2.4%
		% of Total	0.4%	0.4%	1.7%	2.4%
		Adjusted Residual	-1.7-	-1.1-	2.8	
	Not done	Count	182	134	141	457
		% within Yrs	89.7%	83.2%	78.8%	84.2%
		% of Total	33.5%	24.7%	26.0%	84.2%
		Adjusted Residual	2.7	-.4-	-2.4-	
	NORMAL	Count	6	7	14	27
		% within Yrs	3.0%	4.3%	7.8%	5.0%
		% of Total	1.1%	1.3%	2.6%	5.0%
		Adjusted Residual	-1.7-	-.4-	2.1	
Total		Count	203	161	179	543
		% within Yrs	100.0%	100.0%	100.0%	100.0%
		% of Total	37.4%	29.7%	33.0%	100.0%

**Table 6.** Distribution of Colposcopy findings across age groups. N=543.

	Age Group		
	40 Yrs. or less	>40 to 60 Yrs.	>60 Yrs.
CIN1.	7 (2.7%)	11 (4.9%)	3 (5.0%)
Koilocytes +ve.	9 (3.5%)	14 (6.3%)	2 (3.3%)
LSIL.	8 ( 3.1%)	5 (2.2)	0
Not done/required	223 (85.8%)	180 ( 80.7%)	54 (90%)
Normal (-Ve).	13 ( 5%)	13 (5.8%)	1 (1.7%)

colposcopy and directed biopsy, 5% had negative results (C.I.3.3-6.8) and 3.9% had CIN1 (C.I.2.5-5.3). Koilocytosis was found in 4.6% (C.I. 2.9-6.4) (Table 4). Comparing the incidence of cervical dysplasia (CIN) confirmed by colposcopic biopsy over the study period; it was comparable over the three years with the highest percentage in 2014 (5%).

Most of the CIN cases were diagnosed in the age group between 40 and 60 years (4.9%) and was associated with highest report of Koilocytosis (6.3%) when compared to other age groups (Table 6).

## DISCUSSION

With the introduction of Papanicolaou test (cytology) as a method of screening for cervical cancer, the incidence and mortality from cervical cancer has reduced (Benedet et al., 1992; Nygard et al., 2002; Taylor et al., 2006). Screening can detect premalignant and early stage disease, which if treated can prevent the progression to invasive disease (Benedet et al., 1992; Nygard et al., 2002; Taylor et al., 2006). Cervical cancer is common among women in developing countries with poor survival rate due to late diagnosis and limited access to treatment (Ahmedin et al., 2011). CIN refers to squamous abnormalities and is a premalignant condition of the cervix. Follow up of abnormal Pap test with colposcopic-directed biopsy results in the diagnosis of CIN or cervical cancer (Berkowitz, 2013). It was found that human papilloma virus (HPV) is one of the important etiologic factors for cervical cancer (Schiffman et al., 1933; Kaufman et al., 1977).

Peirson et al. found that cervical screening offers protective benefits and is associated with reduced incidence and mortality of invasive cervical cancer (Peirson et al., 2013; Aklimunnessa et al., 2006). Pap test permits examination of cervical cells (cytology, not tissues) as histologic assessment; it is more sensitive in detecting squamous cell malignancy than adenocarcinoma of the cervix (Schiffman et al., 1933). Appropriate follow up of abnormal pap tests is important to detect premalignant or early stage disease (Stuart et al., 1977; Sung et al., 2000).

Atypical squamous cells of undetermined significance (ASC-US) is the most common abnormal finding reported in a Pap test among other abnormal cervical cytology; accounting for 2.8% (Hormuzd et al., 2013). However, ASC-US carries the lowest risk of invasive cervical carcinoma upon tissue diagnosis (Hormuzd et al., 2013). Dmirtas et al. evaluated colposcopic biopsy results of patients with ASC-US and ASC-H in a retrospective study of 358 women between 2005 and 2011. They concluded that ASC-US cytology may lead to the diagnosis of cervical intraepithelial neoplasia (CIN) and cervical cancer, and should be evaluated by colposcopic cervical biopsy (Demirtas et al., 2015). Tokmak et al. investigated

367 women with ASC-US in Turkey, and found that CIN was higher in premenopausal than postmenopausal women with no cases of invasive cervical cancer detected (Tokmak et al., 2014). A cohort study was performed in Norway to estimate the risk of CIN2/3 or invasive cancer after ASC-US Pap smear. The study reported that Pap smear follow-up after one ASC-US smear does not identify women at risk of CIN2/3 or invasive cervical cancer and recommended the implementation of other diagnostic procedures to improve the screening program (Nygard et al., 2003).

In this study, CIN1 was detected in 3.9% of the study population with ASC-US. A higher risk was found in postmenopausal women: 2.7%, 4.9% and 5.0% for the age groups < 40 y, 40 – 60 y and > 60y, respectively. Katki et al. studied 695,360 cervical cytologies for women aged 30 to 64 years and found that the risk of cervical neoplasia with ASC-US Pap smear is as follows: CIN1 in 6.9%, CIN2+3 in 2.6% and 0.18% for cervical cancer (Hormuzd et al., 2013). In the present study, no cases of CIN2 or CIN3 were detected.

Koilocytosis is a squamous epithelial cell that has undergone a number of structural changes which occurs as a result of infection of the cell by human papilloma virus. In this study, Koilocytosis was found in 25 cases (4.6%), most of which were in women below the age of 60 years.

## CONCLUSION

Atypical squamous cells of undetermined significance may carry a small risk of cervical intraepithelial neoplasia, particularly CIN1. Delaying referral for colposcopic assessment after the second ASC-US showed no negative impact on the outcome.

## Conflict of Interest

There is no conflict of interest

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