

## Cytological screening for cervical cancer among Saudi women in Al-Madenah Al Monawarah

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### Abstract

The main cause of cervical cancer is human papilloma virus (HPV) particularly high risk HPV genotype. Cervical epithelial tissue take long time after infected with HPV to progress into cancer, these premalignant lesions is curable when detected. So screening for epithelial abnormality will reduce the morbidity and mortality rate. This study was screened for cervical malignant and premalignant lesions among Saudi women. A total of 432 cervical specimens collected from patients who attended to Children and Maternity Hospital, during the period from April 2015 to November 2016. The specimens were processed with Liquid-based cytology (LBC) technique and examined under the light microscope. The abnormal epithelial cells were detected in 19(4.4%), the most frequent is low grade squamous intraepithelial lesion(LSIL) diagnosed in 9(2.1%), then high grade squamous intraepithelial lesion(HSIL) in 6(1.4%) and a typical squamous cells of undetermined significance(ASC-US). HPV infection was seen in 2(0.5%)cases free from epithelial premalignant changes, Candida infection and TV infections also observed. The study concluded low incidence of premalignant lesions indicate low prevalence of HPV infection among Saudi Arabia.

**Keywords:** cervical cancer, Pap smear, premalignant cells, LSIL, HSIL, ASC-US, HPV

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## Introduction

Cervical cancer is ranked as the fourth most frequent cancer in women (World Health Organization, 2018a). It remains the second most common in developing countries, particularly among women aged between 15 and 44 years (WHO, 2017)

Information from a few years ago showed that an estimated 445,000 new cases, which constituting 84% of all worldwide new cervical tumors, were recorded in developing countries WHO, 2016. Also, of around 270,000 worldwide deaths from the malignancy in that same period, over 85% occurred in these same nations (WHO, 2016). An approximately 84 Saudi ladies out of 241 that diagnosed with cervical malignancy are dying every year according to HPV Information Centre (Sait et al., 2018).

Human papillomavirus (HPV) infection of the cervix is a sexually transmitted illness and a critical hazard factor for the advancement of cervical intraepithelial neoplasia.

However, only a relatively small percentage of ladies with the infection will develop CIN or invasive cervical cancer. Various factors decide if the disease will advance to CIN or carcinoma, the greatest of which is the HPV genotype causing the infection. In spite of the fact that there are around 100 subtypes of HPV, a small subgroup has a known relationship with cervical dysplasia and carcinoma. HPV subtypes are considered either oncogenic or non-oncogenic (Bosch et al., 2003, Wheeler et al., 2009, de Sanjose et al., 2010; Massad et al., 2013). HPVs are classified into low- and high-risk categories, based on their association with malignant lesions and phylogenetic relationships (Lorincz, et al. 1992; Walboomers, *et al.* 1999). Therefore, progression to precancerous cervical lesions by HPV seems to depend on the infecting virus genotype (HPV types 16 and 18 cause approximately 70% of all cervical cancers worldwide and co-infection with multiple HPV-types. Persistent HPV infection is a prerequisite for progression to high-grade lesions (Koshiol, *et al.* 2008) and HPV infection can result in malignancy if the immune system is not able to clear this virus (Stanley, 2009). In addition, epidemiologic investigation shows that there are numerous risk factors for CIN and cervical cancer, such as young age at first intercourse, multiple sexual partners, cigarette smoking, race, high parity, oral contraceptive use, and low socioeconomic status (Castellsague, *et al.* 2002; Bosch and Sanjose, 2007). Almost all instances of cervical cancer can be owing to HPV infection (World Health Organization, 2018b).

Globocan 2017 (International Agency for Research on Cancer [IARC]), annual report showed evidences that, the worldwide age-specific incidence rate of cervical cancer has been persistently decreasing, likely due to Papanicolaou (Pap) screening (UICC, 2017).

The development of squamous cell carcinoma of the cervix is extending many years, that it preceded by stages of premalignant changes of dysplasia which can be develop into carcinoma in situ if untreated, these stages when identified can be treated by simple remedial procedures and continuing follow up. Therefore the detection of these pre-cancerous cells by Pap smear can prevent advancement of disease which result in reduction of morbidity and mortality rate.

### **Materials and methods**

Forty hundred and thirty two women attended to Children and Maternity Hospital with different age and gynecological symptoms in Al-Madenah during the period from April 2015 to November 2016 were included in this study after they gave their informed consent. Cervical specimens were collected by using modified cytobrush and rinsed into a labeled vial (lable in vial matched with a consent form ) containing 15 ml of PreservCyt® transport medium as quickly as possible by rotating the device in the solution 10 times while pushing against the PreservCyt vial wall. The brush was swirled vigorously to further release material, then brush was discarded.

The samples in the preservative fluids were processed according to the manufacturer's directions, Operator's Manual – PrepStain Slide Processor – 780-13000-00. Rev C. Burlington, NC: TriPath Imaging Inc; 2005(Beckton, Dickson and Company). After slide stain processor completed , the sildes rack was removed from prepstain and residual alcohol was decanted, settling chambers also removed and discarded. Then smears were cleared in xylene and mounted with DPX.

### **Results**

A total of 432 cervical smears were investigated cytologically. The age of study group ranged from 15 to 90 with the mean age was (43.2±12.28) and the most of study group at age group 40-49 and 30-39 year (Table 1).

The cytological assessment of Pap smear revealed low incidence of premalignant cells, which constitute 19 (4.4%) of cases, are classified as follows; 6(1.4%) cases were represented HSIL, 9(2.1%) were LSIL and 4(0.9%)ASC-US. However HPV infection was seen in 2(0.5%) cases free for premalignant changes. Majority of cases 192(44.4%) were diagnosed with inflammation, other 28(6.5%) with hormone effect, 7(1.6%) with *candida* and 1(0.2%) with *Trichomonas vaginalis* (Table 1, Figures 1, 2, 3 and4).

The description of cytological results compared to age as shown in table (1). Most of premalignant cells were detected in age group ranged (40-49) followed by 50-59 with account of 9(2.1%) and 4(0.9%) respectively, while other 6 cases were distributed equally at age group 20-29, 30-39 and age group more than 59; 2(0.5%) cases for each. However the majority of inflammation were detected in age between 20 and 50years. These results are statistically insignificant (p value 0.560).

**Table 1. Description of cytological results in relation to age group among study population**

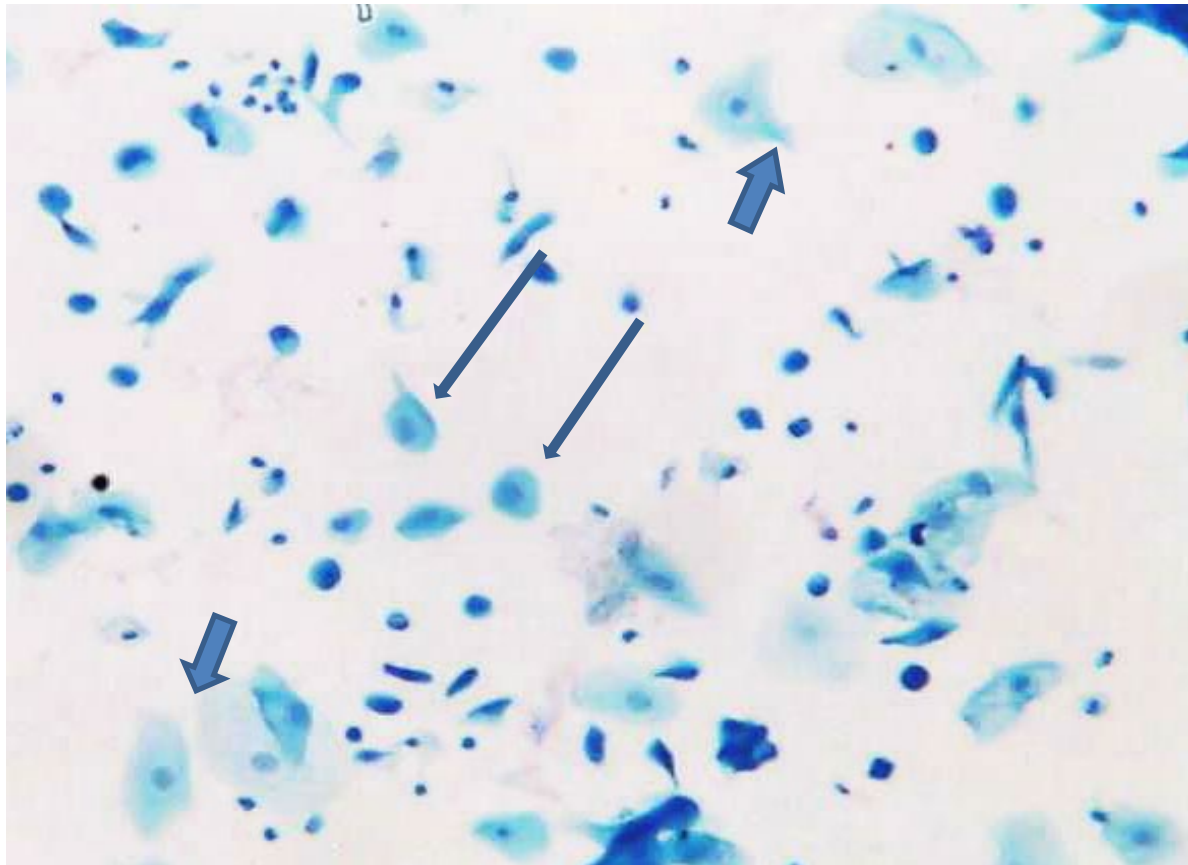
Age group	Cytological results										Total
	Normal	Negative for intraepithelial lesion or malignancy (NILM)						Epithelial cells abnormalities			
		Inflammation	Estrogen effect	Progesterone effect	Trichomonas	candida	HPV	ASC-US	LSIL	HSIL	
Less than 20	2	0	0	0	0	0	0	0	0	0	2
20-29	24	28	8	5	0	2	0	2	0	0	69
30-39	55	55	3	5	0	2	0	0	1	1	122
40-49	51	58	3	3	1	3	1	1	6	2	129
50-59	31	38	0	1	0	0	1	1	1	2	75
More than 59	20	13	0	0	0	0	0	0	1	1	35
Total	183	192	14	14	1	7	2	4	9	6	432

P value p value 0.560

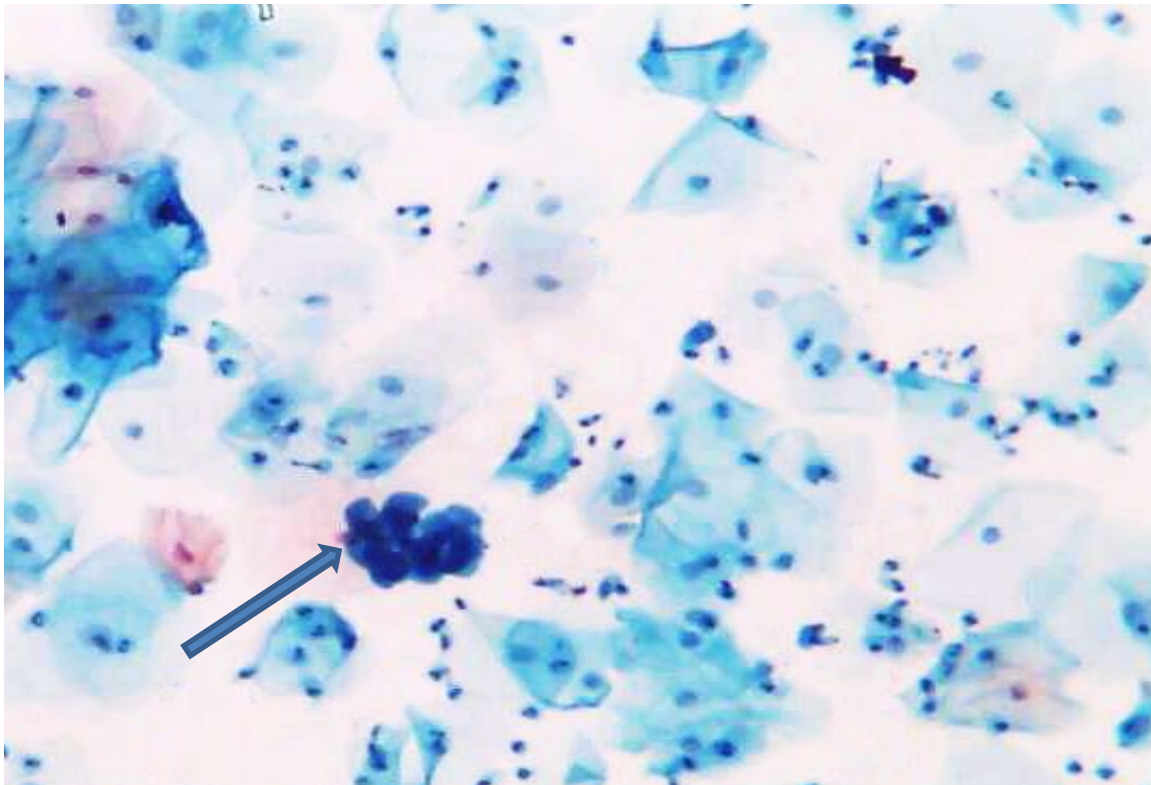
ASC-US=Atypical squamous cells of undetermined significance

LSIL: low-grade squamous intraepithelial lesion

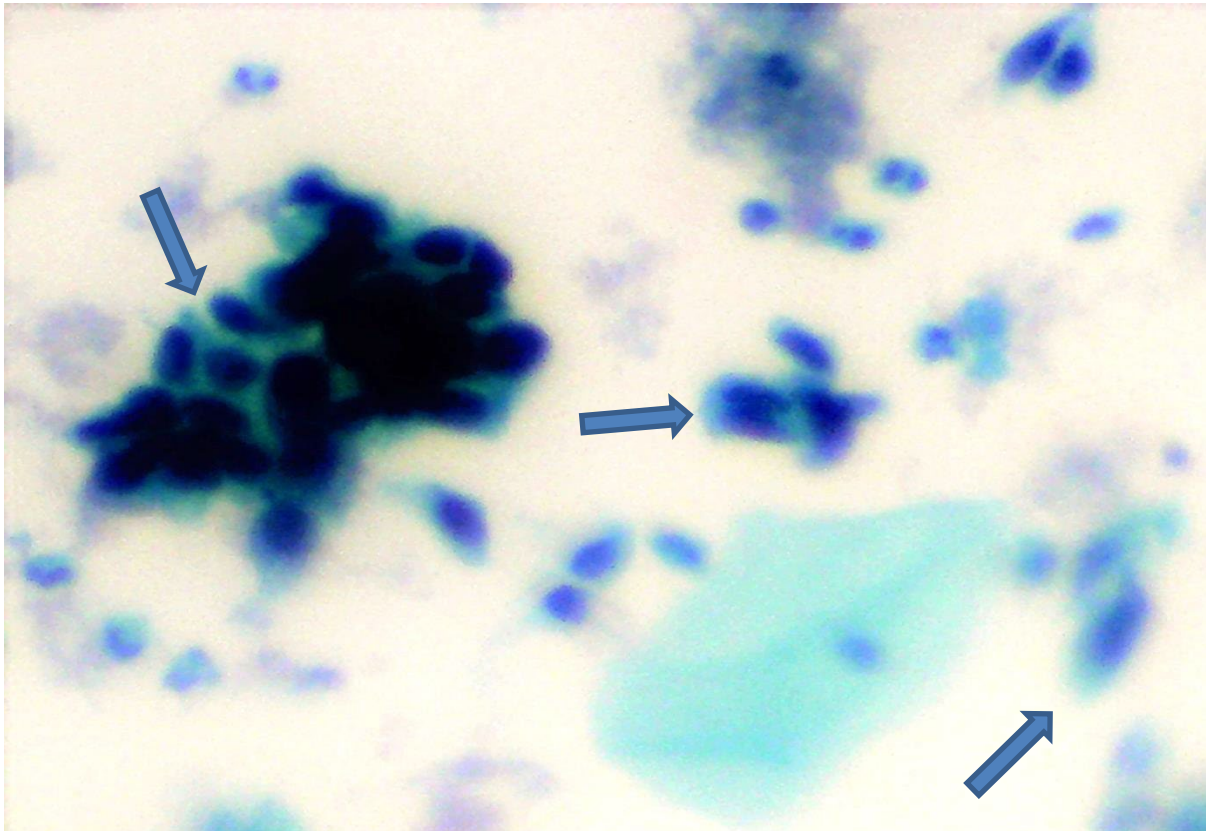
HSIL: high-grade squamous intraepithelial lesion



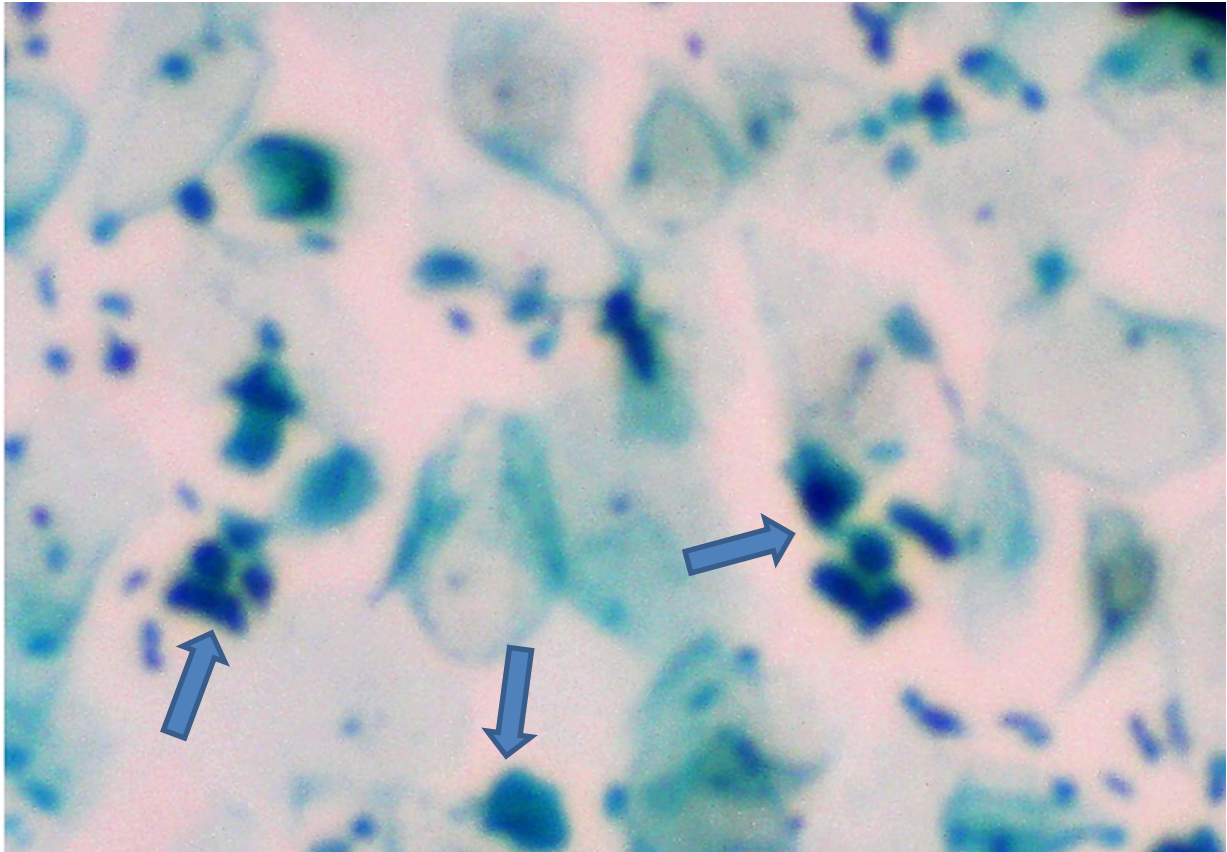
**Figure 1. Cervical smear of 41 years old woman with LSIL shows squamous cells with nuclear enlargement plentiful, thin, translucent cytoplasm with angular borders (long arrow) with Koilocytic change(short arrow). (liquid-based ThinPrep Papanicolaou, X40).**



**Figure 2. Cervical smear of 42 years old woman with LSIL shows cluster of intermediate cells with nuclear enlargement and hyper chromatic (liquid-based ThinPrep Papanicolaou, X40).**



**Figure 3. Cervical smear of 30 years old women with HSIL shows single and clusters of aggregated cells with high nuclear/cytoplasmic ratio, nuclear hyper chromasia with coarse granular chromatin and irregular nuclear membrane(liquid-based ThinPrep Papanicolaou, X40).**



**Figure 4. Cervical smear of 46 years old women with HSIL shows squamous cells with high nuclear/cytoplasmic ratio, nuclear hyper chromatic, vary in size and shape and irregular border (liquid-based ThinPrep Papanicolaou, X40).**

## **Discussion**

The present study showed that the incidence of premalignant cells is low, which constitute 4.4% (19/432) of study cases. This result is similar to previous studies performed in Asia countries, where the rate was accounted for as 4.3% in Saudi Arabia (Al-Kadri et al., 2015), 4.4% in



Kuwait (Kapila et al., 2015), 4.04% in Iran (Maleki et al., 2015), 3.5% in United Arab Emirates, (Krishnan and Thomas, 2016) and 5.9% in Qatar (Elmi et al., 2017) and 3.8% in Jordan (Bayan et al,2017). However low incidence(2.5%) in Saudi Arabia was reported by Azza, 2015 who studied the abnormal cervical cytology for the period from 2004-2013), also similar rate were recorded by HPV Information Centre( ICO/IARC,2019), these variation in incidence in Saudi Arabia may attributed to difference in sample size. Nevertheless all these rates in studies above were low which reflect the Islamic restrictions where there is low prevalence of HPV infection. Out of 19(4.4%) abnormal epithelial cells, the most frequent epithelial cell abnormalities was low grade squamous intraepithelial lesion(LGSIL) constituting 9(2.1%), followed by high grade squamous intraepithelial lesion(HGSIL) 6( 1.4%) and remaining 4(0.9%) were Atypical squamous cells of undetermined significance (ASC-US). These results not far away from Durowade and his colleague (2012), who studied Prevalence and risk factors of cervical cancer among women in an urban community of Kwara State, north central Nigeria, they reported that only 10 (5.0%) respondents had positive cytology result, while the rest were normal. Of the 10 positive cytology results, 1 (0.5%) was HGSIL while the remaining 9 (4.5%) were LGSIL . The results also agrees with Mansour et al, 2013, who reported that the abnormal pap smear was detected in 30/400(7.5%) cases, among which; LGSIL (mild dyskaryosis) was present in 18(4.5%), HGSIL (moderate dyskaryosis +severe dyskaryosis) 11(2.8) and cervical glandular intraepithelial neoplasia (CGIN) was found in one case(0.3%). In present study ASC-US was reported in 4(0.9%) cases this rate approved with other study in Jordan performed by Malkawi et al., 2004, which was (0.8%). Whereas other previous studies was recorded higher rates as in Saudi Arabia by Al-Kadri et al.,2015; Kuwait by Kapila et al., 2015 and United Arab Emirates by Krishnan and Thomas, 2016 , which constitute 2.5%, 2.2% and 1.4% respectively.

In this study the most frequent epithelial abnormalities presented in age groups above 40 years (15/19; 78.9%), the peak at age group 40-49 (9/19; 47.4%), followed by age group 50-59(4/19, 21.1%,) and 2/19(10.5%) for each of 20-30, 30-39 and the age more than 59years. The low incidence of epithelial abnormality at age group less than 40 years reflect the Islamic restrictions, as opposite results detected in non-Islamic countries like studies that performed in United Kingdom and England which proved that there are two peaks in the age-specific incidence rates: the first in women aged 30-34 and the second in women aged 80-84. The earlier peak is related to many women becoming sexually active in their late teens/early 20 years (Tripp

and Viner, 2005; Foley, et al. 2011). While high incidence in women at age more than 40 years may due to the fact that cancer increase with age.

The present finding agrees with estimation in Nigeria (with some difference in age group distribution) recorded, that the inclusion of cervical malignancy screening by age were 1.8% for patients with age group 25–34, 6.6% for those 35–44, 12.7% for those 45–54, and 2.8% for those 55–64year(WHO, 2017). On other hand, according to HPV Information Centre (ICO/IARC,2019) report, the cervical cancer is mostly present in Saudi women between 15 and 44 years of age(Bruni et al., 2019). Also in the present study the majority of ladies with LSIL 8/9(88.9%) were at age above 40 years, and equal distribution of females with ASC-US at age less and more than 40 years. These findings totally disagree with examination in Southern Stockholm revealed that, women with ASC-US were older than women with LSIL; 38% of women with ASCUS were 40 years or older, compared with 21% of women with LSIL(Brismar-Wendel et al ;2009). Further, studies in Saudi Arabia: in central region conducted by Al-Kadri et al.(2015), who found significant higher proportion of squamous cell abnormalities presented in the age groups younger than 40 years compared with the older age groups (older than 60 years). And most common abnormality presented in all the age groups was ASC-US (65%), followed by LSIL (20%). And in Western Saudi Arabia Performed by Altaf and Mufti (2012), their results showed high incidence of epithelial abnormalities 17.3% categorized as ASC-US 9.3%, ASC-H 0.8%, LSIL 2.7%, and HSIL 0.9%. And the mean incidence age of all epithelial abnormalities were at age 40years and above, which not far for the present finding with regardless of epithelial abnormalities rate and their classification which is totally different. The variations in results in these studies above may attributed to the sample size, other probability is study region as the prevalence of HPV is vary from nation to other likewise might be different from territory to other within same country.

## Conclusions

The incidence of premalignant cells was low, which suggest low prevalence of HPV among Saudi women in Al-Madenah Al monawarah particularly HR-HPV, also study noticed that most of epithelial cells abnormalities were seen at women older than 40 years which illustrate that cancer is rarely occur in younger women.

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