

RESEARCH ARTICLE

Prevalence of Abnormal Pap Smears: A Descriptive Study from a Cancer Center in a Low-Prevalence Community

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Abstract

Background and aims: Cervical cancer is the fourth most common cancer in women worldwide and the 13th in Jordan. The cervical smear (Pap smear) is a simple approach to detect pre-cancerous cervical lesions. The aim of this study was to evaluate the prevalence of abnormal cervical smears in women seen at the Early Detection/Community Outreach clinic of King Hussein Cancer Center (KHCC). **Materials and Methods:** In this retrospective study, reports of routine cervical Pap smears performed in the pathology department at KHCC from January 2007 to December 2016, were reviewed. During this period, a total of 5,529 routine smears were assessed for epithelial abnormalities and histopathological grading. **Results:** A total of 210 (3.8%) abnormal Pap smears were found, with atypical squamous cell of undetermined significance (ASC-US) reported in 110 (52.4%) cases, atypical glandular cells of undetermined significance (AGUS) in 58 (27.6%), low grade squamous intra-epithelial lesion (LSIL) in 27 (12.9%) and high grade intra-epithelial lesion (HSIL) in 13 (6.2%). Only single cases of ASC-H and squamous cell carcinoma were reported. The available biopsies showed benign findings in 70.1% of cases, low grade squamous intraepithelial lesions in 11.5% and high grade squamous intraepithelial lesions in 18.4%. **Conclusions:** The low epithelial cell abnormality (EPCA) prevalence illustrated in this study argues against introduction of population-based HPV testing and vaccination. It calls for a more cost-effective measures in a country with limited resources, where a more widely available Pap-smear testing might suffice.

Keywords: Pap smear- abnormal- ASC-US- dysplasia- positive predictive value

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Introduction

The latest worldwide estimates in 2012 showed that cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases (WHO, 2012). There were an estimated 266,000 deaths from cervical cancer worldwide, accounting for 7.5% of all female cancer deaths. About 90% of cervical cancer deaths occur in less developed countries (WHO, 2012). It is believed that most of cervical cancer cases are attributed to 13 high risk HPV types with HPV16 and 18 being the most frequently encountered, accounting for about 70% of cervical cancer worldwide (Stewart and Wild, 2014). In Western Asia, about 2.3% of women in the general population are estimated to harbor cervical HPV 16/18 infection at a given time, and 72.4% of invasive cervical cancers are attributed to HPV 16 or 18 (Bruni et al., 2016). Fortunately, cervical cancer is largely a preventable disease. About 90% of cervical cancers could be prevented by implementation of regular screening program and HPV vaccination (Centers for Disease

Control and Prevention, 2014).

The cervical smear (Pap smear) is a simple test that involves scraping a sample of epithelial cells from the cervical transformation zone using a spatula. The primary aim of the cervical smear test is to detect pre-cancerous lesions, when proper management could be offered before the development of invasive cancer (Safaeian et al., 2007).

Organized cervical screening by Pap smear testing led to dramatic decrease in the incidence and mortality from cervical cancer in developed countries (Centers for Disease Control and Prevention, 2014). This reduction has not been possible in most low and middle income countries largely due to the lack of a systemic screening program (WHO, 2012).

Jordan is classified as an “lower middle income country”. In Jordan, cervical cancer ranks as the 13th most common cancer among women, accounting for 1.5% of female cancer in all ages (Ministry of Health, 2013). Data is not yet available on the HPV burden in the general population of Jordan. However, Pap smear screening is offered mostly on an opportunistic basis in gynecological

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and family planning clinics. Although 50-75% of women in Jordan have heard about the Pap smear as a mean to detect cervical cancer, only 15-40 % have ever been screened (Amarin et al., 2008; Barghouti et al., 2008; Department of Statistics [Jordan] and ICF International, 2013; Al Rifai and Nakamura, 2015). Furthermore, more than half of Jordanian gynecologists questioned the cost effectiveness of cervical smear test and one third were not requesting Pap smear testing for their patients (Lataifeh et al., 2009).

The current study was conducted to evaluate the prevalence of abnormal cervical smear in women seen at the Early Detection/ Community Outreach Clinic at King Hussein Cancer Center (KHCC), and to investigate any change in the prevalence of abnormal Pap smear over time. This might help to guide future direction into the need for a national screening program for cervical cancer, and additional preventive measures including HPV testing and HPV vaccination.

Materials and Methods

This is a retrospective cohort study based on a review of the reports of cervical Pap smears performed in the pathology department at King Hussein Cancer Center (KHCC) from January 2007 to December 2016. After obtaining the approval from the Institutional Review Board, all Pap smear files as well as surgical pathology files were searched for “routine” Pap smears. During this period, conventional Pap smear tests were used in the first 8 years (2007–2014), whereas in the last 2 years both conventional and SurePath slides were evaluated simultaneously for each case. Abnormal routine Pap smears were classified according to latest Bethesda system into the following categories: Atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude high grade squamous intraepithelial lesion (ASC-H), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma (SCC), atypical glandular cells of undetermined significance (AGUS), and adenocarcinoma (ADC). For each abnormal Pap smear, correlation with tissue biopsy from the cervix if available was also performed. The presence and the grade of dysplasia as well as the utility of immune stains performed on tissue biopsy especially P16 (Clone E6H4, ready to use, Roche) and HPV-16 (Clone Cam Vir-1, ready to use, BioGenex) in confirming or ruling out HPV infection were collected when available. P16 testing was not done on the Pap smear of the Surepath cases.

Excel sheet version (2013) was used for data analysis. Descriptive statistics using frequencies and percentages were applied for Pap smear and cervical biopsy results. While positive predictive value of our Pap smear results (probability of having the dysplasia with positive Pap smear results after definite diagnosis with cervical biopsies) was calculated using the following equation. $PPV = \frac{\text{number of patients having cervical dysplasia and had abnormal Pap smear}}{\text{Number of patients having cervical dysplasia and had abnormal Pap smear} + \text{Number of patients who do not have cervical dysplasia and had}}$

abnormal Pap smear result.

Results

During the 10-year period a total of 13,093 Pap smears were reported. Of these, 5,529 (42.2%) were routine Pap smears performed as a screening test, and the rest were for follow up of diagnosed cervical and endometrial cancer patients. The latter cases were excluded from further analysis. Of the routine smears, there were a total of 210 (3.8%) abnormal Pap smears. The most frequent epithelial cell abnormalities were ASC-US reported in 110 (52.4%) cases, followed by AGUS in 58 (27.6%) cases. Out of the 210 abnormal smears, there were 27 (12.9%) LSIL and 13 (6.2%) HSIL cases, respectively. Only a single case of

Table 1. Yearly Analysis of Pap Smear Diagnoses from 2007 to 2016

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Total Pap smears	965	1227	1309	1360	1380	1355	1288	1355	1312	1542	13093
Routine Pap	716 (74.0)	844 (64.5)	726 (55.5)	454 (33.4)	523 (37.9)	657 (48.5)	355 (27.6)	426 (31.4)	221 (16.8)	607 (39.4)	5529
EPCA	16 (2.2)	37 (4.4)	32 (4.4)	10 (2.2)	18 (3.4)	41 (6.2)	18 (5.1)	6 (1.4)	14 (6.3)	18 (2.9)	210 (3.8)
ASC-US	9 (1.26)	19 (2.25)	19 (2.6)	4 (0.88)	9 (1.72)	20 (3.04)	13 (3.7)	1 (0.23)	10 (4.5)	6 (1)	110 (2)
ASC-H	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.16)	1 (0.02)
LSIL	6 (0.84)	6 (0.7)	4 (0.55)	1 (0.22)	0 (0)	8 (1.2)	1 (0.3)	0 (0)	1 (0.45)	0 (0)	27 (0.5)
HSIL	0 (0)	0 (0)	2 (0.27)	1 (0.22)	5 (0.96)	2 (0.3)	1 (0.3)	0 (0)	2 (0.9)	0 (0)	13 (0.23)
SCC	0 (0)	0 (0)	1 (0.14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.02)
AGUS	1 (0.1)	12 (1.4)	6 (0.83)	4 (0.88)	4 (0.76)	11 (1.67)	3 (0.8)	5 (1.2)	1 (0.45)	11 (1.8)	58 (1.05)

Figures in parentheses give the percentage with respect to the number of routine Pap.

Table 2. Biopsy Correlation with Abnormal Pap Smears (2007-2016)

Pap smear diagnosis	# cases	Pathology Correlation	Benign	Low Grade	High Grade
ASC-US	110	44	31 (70.5)	7 (16%)	6 (13.5)
ASC-H	1	1	0 (0)	0 (0)	1 (100)
LSIL	27	14	10 (71.5)	3 (21.5)	1 (7)
HSIL/SCC	14	8	4 (50)	0 (0)	4 (50)
AGUS/ ADC	58	20	16 (80)	0 (0)	4 (20)
Total	210	87	61 (70.1)	10 (11.5)	16 (18.4)

Numbers in parentheses give the percentage with respect to the number of pathology correlation.

Table 3. Biopsy Correlation and P16 Immunostains Results for Abnormal Pap Smears (2007-2016)

Pap smear diagnosis	# cases	Pathology Correlation	Total P16 immunostain	Positive	Negative
ASC-US	110	44	36	12 (33)	24 (77)
ASC-H	1	1	1	1 (100)	0 (0)
LSIL	27	14	9	4 (44)	5 (56)
HSIL	14	8	7	3 (43)	4 (57)
AGUS	58	20	5	2 (40)	3 (60)
Total			58	22 (38)	36 (62)

Figures in parentheses give the percentage with respect to total P16

ASC-H and squamous cell carcinoma, respectively, were reported. Table-1 shows the distribution of abnormal Pap smears during the study period.

A total of 87 cervical biopsies for abnormal Pap smears were reported at KHCC. The results of cervical biopsies were benign findings in 61(70.1%) cases; low grade squamous intraepithelial lesion in 10 (11.5%) and high grade squamous intraepithelial lesion in 16 (18.4%) cases. Table 2 summarizes the biopsy findings in correlation with the different reported Pap smear categories. The overall positive predictive value of the Pap smear cytology diagnosed at KHCC was 30%.

For the available tissue biopsies, P16 immunostain was performed on 58 cases. There were 22(38%) positive cases and 36 (62%) negative cases. HPV-16 immunostain was performed on 28 biopsies. Positive results were reported in 5 (17.8%) cases. Three of which were diagnosed as LSIL on Pap smear, with the other two cases diagnosed as ASCUS and HSIL. Tables 3 and 4 summarize the findings of P16 and HPV-16 immunostains in available biopsies, respectively.

Discussion

The incidence of cervical cancer is more common in less developed compared to more developed countries

with age-standardized rate of 15.7 per 100,000 and 9.9 per 100,000, respectively(World Health Organization, 2012). Jordan has one of the lowest rates of cervical cancer across all Western Asia countries with age-standardized rate of 2.4 (Bruni et al., 2016). Around 50 new cases of cervical cancer are diagnosed annually in Jordan (Ministry of Health, 2013). Of these 70-80% are presented to and treated at KHCC, being the only national referral cancer center.

This article reported a low frequency of abnormal Pap smear of 3.8% , which would be concordant with the low prevalence of cervical cancer in WHO Eastern Mediterranean Region (WHO, 2012). This low frequency is probably a reflection of sexual behavior governed by religious and cultural values in such a conservative country.

Epithelial cell abnormality (EPCA) of 3.8% in the current study is comparable to similar studies performed in Middle East countries where the rate was reported as 4.4% in Kuwait, 3.5% in United Arab Emirates, 5.9% in Qatar, and 4.3% in Saudi Arabia (Al-Kadri et al., 2015; Kapila et al., 2015; Krishnan and Thomas, 2016; Elmi et al., 2017). Supporting the effect of religious restrictions, similar rates were also seen in studies performed in Islamic countries with a rate of 4.04% in Iran and even as low as 0.2 % in Turkey (Daloglu et al., 2014; Maleki

Table 4. Biopsy Correlation and HPV-16 Immunostain Results for Abnormal Pap Smears (2007-2016)

Pap smear diagnosis	# cases	Pathology Correlation	Total HPV-16 immunostain	Positive	Negative
ASC-US	110	44	19	1 (5)	18 (95)
ASC-H	1	1	1	0 (0)	1 (100)
LSIL	27	14	3	3 (100)	0 (0)
HSIL	14	8	4	1 (25)	3 (75)
AGUS	58	20	1	0 (0)	1 (100)
Total			28	5 (18)	23 (82)

Figures in parentheses give the percentage with respect to total HPV-16 immunostain.

et al., 2015). On the other hand, the rate of cervical smear abnormalities is higher in high risk areas and in areas with higher prevalence of HPV infection. This includes Russia, in which a rate of EPCA as high as 9.8%, India with rate of 10.8% and South Africa with rate of 17.3%, were reported (Singh and Singh; Shipitsyna et al., 2011; Richter et al., 2013). Interestingly; our EPCA rates were higher than that in other studies reported in Jordan, in which rates as low as 1.6% and 1% were reported (Dajani et al., 1995; Malkawi et al., 2004)

The ASC-US diagnostic category which describes cellular abnormalities that are more marked than those attributable to reactive changes but that quantitatively or qualitatively fall short of a definitive diagnosis of low-grade squamous intraepithelial lesion (Solomon and Nayar, 2004), remains a subjective category with threshold that varies among individual pathologists. It is the most common epithelial abnormality reported in our Pap smear results. Guidelines conclude that a rate of greater than 5% might constitute misuse of the term (Davey et al., 1994). In our study ASC-US rate was acceptable, as it represented 2% of all reported routine Pap smears. However, this rate is almost double the rate of a previous study performed in Jordan with a rate of 0.8% (Malkawi et al., 2004). This is probably a reflection of a lower threshold among our pathologists being affiliated with a cancer center. On the other hand, a similar and comparable rate of ASC-US was reported in other studies which were performed in low risk regions, such as a rate of 2.2% in Kuwait (Kapila et al., 2015), 1.4% in United Arab Emirates (Krishnan and Thomas, 2016), and 2.5% in Saudi Arabia (Al-Kadri et al., 2015). In comparison; ASC-US reporting rate was higher in Russia and South Africa with a rate of 7.2% and 4.7, respectively (Shipitsyna et al., 2011; Richter et al., 2013).

The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for management of ASC-US cases with no HPV result is to repeat cytology at 1 year and if ASC-US persists or progressed into other categories, then colposcopy with endocervical sampling of any lesion is recommended (Massad et al., 2013). In our study, 31 out of 44 ASC-US cases with biopsies had benign findings, while 13 (29.5%) cases had cervical dysplasia. These results are close to a study performed by Barcelos, et al., who analyzed patients with ASC-US and reported dysplasia on tissue biopsy in 14.6% of cases (Barcelos et al., 2011). AGUS was the second most commonly encountered category, which accounted for 1.05% of all routine Pap smears. This is comparable to the incidence of AGUS category (0.8%) which was reported from Kuwait (Kapila et al., 2015). The rate in UAE and Saudi Arabia was much lower with 0.05% and 0.27%, respectively (Al-Kadri et al., 2015; Krishnan and Thomas, 2016). Similarly in a study performed to determine the clinical significance of AGUS, 24.8% of patients with AGUS abnormality had pre-neoplastic or neoplastic, squamous or glandular lesions on tissue biopsy (Chhieng et al., 2000). In this study, a follow up biopsy of AGUS cases showed cervical dysplasia in 20%. With the lack of national guidelines for the management of abnormal Pap smears in Jordan, a close follow up of ASC-US and

AGUS cases is warranted.

As for squamous dysplasia, the LSIL rate of 0.5% is double the rate of 0.02% that was previously reported from Jordan (Malkawi et al., 2004). As LSIL indicates viral cytopathologic changes of HPV infection, our results suggest a slight increase in the overall rate of HPV infection in Jordan. However, our results are still lower than high prevalence areas and are comparable to the rate of such abnormality reported in regional studies in Kuwait, UAE and Saudi Arabia where the prevalence of LSIL was 0.95%, 1.8% and 0.86%, respectively (Al-Kadri et al., 2015; Kapila et al., 2015; Krishnan and Thomas, 2016). In comparison; the rate is much higher in Russia (2.5%) and South Africa (3%) (Shipitsyna et al., 2011; Richter et al., 2013). Additionally, the rate of 0.23% and 0.02% for HSIL and SCC, respectively, and is consistent with rates reported in Kuwait (0.22% and 0.09%, respectively) and Saudi Arabia (0.22% and 0.04%, respectively) (Al-Kadri et al., 2015; Kapila et al., 2015).

In assessing the correlation between Pap smear cytology and the results of cervical biopsy; P16 and HPV-16 immunostains were used in a subset of cases with available biopsies to support the final diagnosis. P16 is a cyclin-dependent kinase inhibitor which is over expressed in cells infected by high-risk HPV and is negative in normal cervical squamous epithelium (Miller, 2002). Bose et al., (2005) reported P16 staining in 36% of abnormal pap smears. In our cohort P16 reactivity was seen in 38% of cases in total, and it was used to support the diagnosis of cervical dysplasia. We used HPV-16 immunostain to detect infection with the most common high risk HPV subtype, HPV-16 as a cause of cervical dysplasia and cervical cancer (Stewart and Wild, 2014), and our results are comparable to that reported in the literature. (Bose et al., 2005)

The overall positive predictive value (PPV) of Pap smear cytology diagnosed at KHCC was 30%. Literature review shows a high variability with a range from 17-89%. A study from Turkey reported a PPV of 26% (Barut et al., 2015). Another study in Sudan reported a PPV of 87.5% (Ibrahim et al., 2012). Several studies from India reported variable PPV ranging from 22-97.5% (Hegde et al., 2011). This relatively low PPV might indicate a more cautious approach from our reporting pathologists. Overcalling trivial abnormalities that might be over looked in other settings where pathologists more frequently encounter HPV related abnormalities might be a plausible explanation.

We acknowledge the limitations of our study. All samples have been retrieved from a single institution and the number of cervical biopsies performed for abnormal Pap smears is low. Some of these biopsies might have been performed and the patients might have been managed accordingly outside KHCC. However; this study provides an update on the status of Pap smear findings in general and abnormal findings in particular in our population.

Based on the low rate of abnormal pap smears provided, the low prevalence of cervical cancer in Jordan, acknowledging that the positive predictive value of a single HPV test is around 20% for precancerous and even less for cancer (Centers for Disease Control and

Prevention, 2014), and that HPV and Pap co-testing is associated with more false-positive results than the Pap test alone which might lead to more frequent testing and invasive procedures (Moyer, 2012), we believe that screening women with Pap smear test without HPV co-testing remains an acceptable and adequate practice in Jordan. Promoting Pap smear testing among the gynecologists and general practitioners might be a more cost effective model in the setting of a low prevalence country. Additionally, HPV vaccination might not be warranted or justified in such a setting.

In conclusion, we reported our experience with more than 5,000 routine Pap smears. The rate of abnormal smears was only 3.8%. The most common reported abnormality was ASC-US followed by AGUS, with a biopsy proven dysplasia of 29.5% and 20.0%, respectively. This low prevalence of EPCA argues against a population-based HPV testing and vaccination. It calls for more cost-effective measures in a country with limited resources, where a more widely available Pap-smear testing might suffice.

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