

The yield of pap smears and its characteristics in a community based setting in Saudi Arabia

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ABSTRACT

Objectives: To assess the yield of Papanicolaou tests (pap smears), including the characteristics of abnormal pap smears.

Methods: In this record-based cross-sectional study, we reviewed pap smears of patients seen at the Family Medicine clinics, King Faisal Specialist Hospital and Research Center from January 2002 to January 2017. All women between the ages of 21 and 65 were included. Study-specific case report form was developed to capture patient demographics, pap smear histopathology (Bethesda III System), human papilloma virus polymerase chain reaction (HPV PCR), and the parity status.

Results: A total of 3346 patients were included; 2.2% had abnormal pap smear. Most frequent abnormalities were atypical squamous cells of undetermined significance (2%), followed by glandular cell abnormalities (0.8%). Human papilloma virus infection was detected in 6.5% and all other infections were identified in 9.2% of all screened Pap smears.

Conclusion: Pap smears remain an effective tool for cervical cancer screening. Low yields of pap smears compared to other developed countries could be attributed to lower risk factors for cervical cancer in Saudi Arabia. Routine screening especially among high risk women is strongly recommended.

Keywords: pap smear, primary care, Saudi Arabia, HPV, cervical cancer

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Cervical cancer is the 4th leading cancer among women worldwide, with an estimated 570,000 new cases in 2018.¹ The incidence of cervical carcinoma is higher in underdeveloped countries. Approximately 90% of deaths from cervical cancer occur in low- and

middle-income countries (LMICs). In the United States of America (USA), cervical carcinoma is the 14th most common gynecologic cancer.² Saudi Arabia has a population of 9.29 million women who are at risk of developing cervical cancer. Cervical cancer ranks as the 10th most common cancer among women in Saudi Arabia, and the 7th most frequent cancer among women between the ages of 45 and 59 years old.³ The reported incidence rate of cervical cancer in Saudi Arabia is derived mainly from the Saudi Cancer Registry data and a few hospital-based studies.

Pap smear is the gold standard for cervical cancer screening to reduce mortality by early detection of precancerous lesions. Human papilloma virus (HPV) infection is one of the most significant risk factors for cervical cancer.^{1,4} Precancerous cervical lesions and cervical carcinomas are markedly associated with HPV infections.¹ Human papilloma virus-16 and HPV-18, are classified as “high-risk types” and are associated with most of the cervical cancers, globally.⁴ Human papilloma virus genotypes 16/18 are associated with cervical intraepithelial neoplasia (CIN) II-III and invasive cancers in regional studies.⁵ These infections are associated with significant morbidity, complications, and costly treatment. Screening for cervical cancer includes pap smear cytology alone or co-testing for HPV infection. United States Prevention Service Task Force (USPSTF) for cervical cancer screening recommends that women aged 21 to 65 years should be screened with a pap smear every 3 years.⁶ Women between the ages of 30 and 65 may receive a combination screening of a pap smear and HPV test every 5 years.⁶

Cervical cancer screening recommendations are being reviewed continuously based upon new information about HPV and emerging technologies. Yearly screening of cervical cancer with pap smears was routinely carried out in USA over the last several decades following its introduction. However, recommended intervals between screenings were increased, subtly. The USPSTF issued new recommendations against yearly cervical cancer screening and more than 20 medical organizations led by the American Society for Clinical Pathology, American Society for Colposcopy and Cervical Pathology, and American Cancer Society.⁶ Current recommendations are to screen for cervical cancer by pap smear at 3-year intervals or co-testing of pap smear with HPV at 5-year intervals for women between the ages of 30 to 65 years old. Subsequently, the American College of Obstetricians and Gynecologists revised its recommendations for screening pap smears in line with aforementioned guidelines, though with a predilection for 5-yearly co-tests as compared to testing every 3-year.⁷

This study was designed to evaluate the yield of pap smears, including the characteristics of abnormal pap smears in primary care setting. In addition, prevalence of abnormal pap smears, cervical infections, and cervical cancers was determined in this first community-based study in Saudi Arabia.

Methods. The record-based cross-sectional study was conducted at Department of Family Medicine and Polyclinics, King Faisal Specialist Hospital and Research Center (KFSH&RC), Riyadh, Saudi Arabia. The primary care services are provided by the Department of Family Medicine to a community of more than 50,000 eligible patients. We reviewed the digital medical records of all the female patients from 21 to 65 years of age for pap smear results between January 2002 and January 2017. There were no exclusions from this group. Pap smears are carried out at these clinics as per the cervical cancer screening guidelines by USPSTF. The electronic medical records information on the pap smear reports, HPV PCR results, and their demographic characteristics (including age, nationality, marital status, and parity status) were collected.

All pap smears were reported as per the 2001 Bethesda III System Terminology. According to Bethesda III, histopathologic abnormalities of pap smears were categorized into atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesion (HSIL), and squamous cell carcinoma (SCC). The ASC cytology was further sub-stratified in 2 sub-groups: ASC-unknown significance (US) and ASC-H (ASC-H, cannot exclude high-grade lesions). Abnormalities of glandular cells encompassed (AGC), endocervical adenocarcinoma in-situ (AIS), and adenocarcinoma.⁸

Study was conducted according to Declaration of Helsinki and National Institute of Health Guidelines. The study was approved by the Research Advisory Council and the Ethics Committee of King Faisal Specialist Hospital and Research Centre (RAC# 2161-086). The Institutional Review Board approved a waiver of informed consent as the medical records were reviewed retrospectively and anonymously ensuing less than minimal risk. There was no interaction with the patients, no clinical intervention, no additional information, tests, or patient contact was needed.

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Statistical analysis. The statistical analysis was carried out using the Statistical Package for the Social Sciences), Windows version 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables of descriptive statistics were stated as means and median, and categorical variables were reported as percentages and frequencies. Student t-test and ANOVA were used to compare continuous variables, while Chi-square test was used to compare categorical variables. Logistic regression was utilized to evaluate the role of potential risk factors for the development of different cytological changes. The level of statistical significance was set at $p < 0.05$.

Results. As per the eligibility criteria, the electronic records of 3346 patients, who underwent pap smear cytology were reviewed. Approximately 55% of patients were Saudi nationals. The mean age of the study population was 47 years (SD [standard deviation] \pm 11.9), and the average parity of women was 3.5 (SD \pm 2.4) children. Abnormal epithelial cells were found in 2.2% (n=74) of pap smears. The most common cytological abnormalities were squamous cell abnormalities (n=69/74 [93.2%]) followed by glandular cell abnormalities (n=5/74 [0.8%]). The HPV test was carried out for only 8.1% (n=274) of the included samples as the HPV test was recently added to our Pathology Lab System. Among those, only 6.6% (n=18) were tested positive for HPV. (Table 1)

A total of 9.2% (n=309) pap smears were tested positive for infectious organisms. Infectious organisms were mostly candida (4.9%), followed by bacterial vaginitis (3.6%). Abnormal epithelial cells were found in 2.2% (n=74) of pap smears. Out of these, 21.6% (n=16) had a history of abnormal epithelial changes in previous smears, while 78.4% (n=58) had no changes. Only 0.6% (n=22) with normal epithelial cytology, had a prior history of abnormal epithelial changes (Table 2). Among patients who were found to have squamous cell

Table 1 - Human papilloma virus status (N=274).

HPV PCR	n (%)
Negative	256 (93.4)
Positive	18 (6.6)
<i>Positive subtypes:</i>	
HPV 16	3
HPV 18, 45	1
HPV 31, 35, 33, 52, 58	2
HPV 39, 68, 56, 66	1
Combined	6
Other	5

HPV PCR: human papilloma virus polymerase chain reaction

abnormalities, ASC-US represented 69.5% (n=48/69) of these abnormalities. In this group, the LSIL was positive in 23.2% (n=16/69), ASC-H was positive in 4.3% (n=3/69), and HSIL were present in 2.8% (n=2/69). Among 6.8% of glandular cells abnormalities, AGC represented 66% (n=3/5), and adenocarcinoma was reported in 40% (n=2/5) of the cases (Table 3).

The logistic regression analysis showed that there was a significant relationship between the presence of epithelial changes with advancing age and with the history of epithelial changes in the previous pap smears ($p < 0.001$).

Discussion. Cancer of the cervix is the 3rd highest gynecological malignancy in Saudi Arabia.⁹ This study established the yield of pap smears to identify women at high risk of cervical cancer among asymptomatic women. Comparative analysis was carried out with other developed countries to evaluate the utility of pap smear as an effective screening tool stratified by independent risk factors. Pap smear remains the primary screening tool for cervical cancer at our center.

We reviewed cytology reports of screening pap smears of women seen at family medicine clinics affiliated with KFSH&RC as compared to yield of pap smears reported by hospital-based setting in specialist clinics, analyzing cases of potentially symptomatic patients referred for further assessment and management.¹⁰⁻¹² Our study was carried out in a community-based setting, giving

a more realistic estimate of the presence of pap smear cytology changes in the population and risk factors for developing intraepithelial lesions of cervix and its correlation with HPV infection in Saudi Arabia.

Analysis of cervical cytology in our protocol exhibited a lower prevalence of abnormal pap smears (2.2%) in reference to other hospital-based studies in Saudi Arabia. In a study done in the Southwestern region of Saudi Arabia (n=2100) 7.9% had epithelial abnormalities; SCC was diagnosed in 7 cases compared to 2 cases in our study.¹⁰ A hospital based study in Western Region of Saudi Arabia (n=7297) reported 17.3% abnormal pap smears.¹¹ Another case-control study done in the Central Region reported 4.3% abnormal Pap smears; 91% had squamous cell abnormalities and 9% were glandular cells abnormalities. Squamous cell carcinoma was detected among 8 patients (1%).¹²

A hospital-based study in Kuwait reported atypical squamous cells of undetermined significance (ASC-US) as the most common epithelial abnormality (2.2%).¹³ A study carried out in Iran reported 1.18% abnormal Pap smears. Overall incidence of cervical cancer among these samples was 0.2%.¹⁴ A large study from Turkey (n=140,334) reported 1.8% cytological abnormalities.¹⁵

In USA, the yearly incidence of cervical CIN1 was reported to be 1.2/1,000, and CIN 2/3 was 1.5/1,000. Out of total number of routine pap smears (44,493), approximately 94.5% were normal and the abnormal diagnosis included 3.3% ASC; 0.2% AGC; 1.2% LSIL; and 0.3% HSIL.¹⁶

The reported incidence of cervical cancer in Saudi Arabia is one of the lowest in the world, including the low reported rate of HPV among the tested samples. The low rate of HPV can be attributed most probably to cultural practices of monogamy, lack of promiscuity, religious practices and adherence to strict moral code. The crude incidence rate of cervical cancer is 2.2 cases per 100,000 women per year in Saudi Arabia, as compared to 3.9 cases in Western Asia.¹ The incidence of cervical cancer from our study is 3.9/100,000 per year, which is higher than the incidence reported by the Saudi Cancer Registry for 2015 at 1/100,000 per year. The poor reporting of cancer cases from the different hospitals and especially from the peripheral regions could explain the low reported incidence rate estimated by the Saudi Cancer Registry.³ Since, our primary care clinics perform routine cervical cancer screening, the probability of detecting asymptomatic cervical cancer is high.

The routine HPV screening commenced much later in our clinics. Therefore, a smaller number of samples were tested for HPV in our study; HPV screening was

Table 2 - Classification according to the presence of epithelial cell abnormality and infectious organisms among the total number of Pap smears (n=3346).

Parameters	n (%)
Presence of infectious organisms only	309 (9.2)
Presence of epithelial cell abnormalities	74 (2.2)
Presence of infectious organisms and epithelial cell abnormalities	3 (0.1)
No infectious organisms or epithelial cell abnormalities	2961 (88.5)

Table 3 - Epithelial cell abnormalities (n=74/3346) grouped based on pathology findings.

Parameters	n (%)
Squamous cells	69 (2.1)
Atypical squamous cells of undetermined significance	48 (1.4)
Atypical squamous cells, cannot exclude high-grade lesions	3 (0.1)
Low-grade squamous intraepithelial lesions	16 (0.5)
High-grade squamous intraepithelial lesions	2 (0.1)
Glandular cells	5 (0.1)
Atypical glandular cells	3 (0.1)
Adenocarcinoma	2 (0.1)

carried out for 8.1% (275/3346) and 6.6% (18/275) had positive results. The prevalence of HPV 16/18 was 2.7% in the cytology of cervical cancer cases in Saudi Arabia.¹ The prevalence of HPV in Saudi Arabia was reported to be 82% as compared to global prevalence (85%-99%) in cervical cancers.⁵ Prevalence of HPV 16/18 among women with cervical cancer in Europe was 74%.¹ Prevalence of any and high-risk genital HPV for adults aged 18 to 59 in USA was 45.2%, 25.1% in men, 39.9%, and 20.4% in women during 2013-2014.¹⁷ Presence of HPV is highly sensitive as compared to cytology alone for diagnosing pre-cancerous lesions (CIN3/AIS) and can help in increasing the interval of screening pap smears, avoiding the risk associated with over-screening. Slightly increased cancer detection can be achieved by the combined testing as compared to HPV testing alone.

Preventing high-risk HPV infection is paramount to the prevention of cervical dysplasia and cancer. Vaccines for the prevention of HPV infection are widely available but still underutilized in Saudi Arabia. This is due to insufficient knowledge and awareness on the natural course of the disease.¹⁸ Since long-term effectiveness of the vaccine is unknown, all women should undergo cervical cancer screening, regardless of vaccination status. Insufficient awareness and knowledge of the importance of cervical cancer screening was the major reason for the lower acceptance of pap smears among Saudi women.¹⁹ Cervical cancer screening may be improved by combining other factors like family history, advanced age, history of previous abnormal cytology on pap smears, and co-morbidities, and so on, in addition to the cytology.

Study limitations. Pap smear test is not widely accepted by Saudi women due to lack of knowledge about the importance of cervical screening. Human papilloma virus screening was carried out on a relatively small proportion of sample population due to late implementation.

In conclusion, yield of pap smears and abnormal characteristics were significantly lower as compared to other developed countries. It could be attributed to lower risk factors, lack of knowledge, insufficient primary prevention, and access to care in Saudi Arabia. Patients with history of abnormal intraepithelial smears are more prone to have subsequent abnormal pap smears. Paucity of data and wide regional variation in the Kingdom warrants a well-structured screening program and age-appropriate screening guidelines for cervical cancer prevention, early detection and effective management.

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