
Low rate of cervical cancer among women with rising incidence of cervical cytological abnormalities. The unlearnt lesson

M.A. Freij¹, M.M. Khadra¹, H.A. Abu Farsakh², H.H. Saleh³, A.A. Ijmail², B.O. Rahal¹,
M.H. Waldali⁴, N.S. Najeeb⁵, L.H. Tahtamouni⁵

¹ Department of Obstetrics and Gynecology, Faculty of Medicine, University of Jordan, Amman

² The First Medical Laboratories, Amman; ³ Elite Moms Clinic, Amman

⁴ Obstetrics and Gynecology Department, Specialty Hospital, Amman

⁵ Department of Biology and Biotechnology, Faculty of Science, The Hashemite University, Zarqa (Jordan)

Summary

Objectives: Cervical cancer is preceded by a group of epithelial cell abnormalities. However, there is insufficient data on cervical abnormalities in Jordan and the Middle East at large. The current study aimed at determining the prevalence of different cytological abnormalities in women in Jordan. In addition, it aimed at assessing the age specific cytological abnormalities in these women and analyzing the changing trends of epithelial cell abnormalities in cervical smear over a period of 15 years compared in three periods of five years each. **Materials and Methods:** 6,455 conventional cervical Papanicolaou (Pap) smear results obtained between January 2000 and December 2014 were retrospectively analyzed. **Results:** Out of the 6,454 Pap smears analyzed, 5,645 (87.5%) were found adequate for reporting. A total number of 801 (14.2 %) cases had cervical epithelial abnormalities. A significant increase in cytological abnormalities was observed between 2000 and 2014. In addition, a significant increasing trend in cervical cytological abnormalities was noted between 2000 and 2014. The highest percentage of cytological abnormalities (20.1%) was found in women younger than 25 years old. In all of the age groups, the low-grade squamous intraepithelial lesions (LSIL) cytological abnormality was the most prevalent. **Conclusions:** Invasive cervical cancer is still a killer for young women in the developing countries. The present study may reflect a change in the socio-sexual behavior over the last 15 years. The current work highlights the importance of awareness campaigns on the importance of cervical smear and the urgent need for initiating a cervical screening program in Jordan.

Key words: Pap smear; Cervical cancer; HPV; Cervical screening program; Jordan.

Introduction

Cancer is the second leading cause of death worldwide. In Jordan, 14.6% of deaths are caused by cancer, ranking second after cardiovascular diseases [1]. Cervical cancer is the second most common cancer in women worldwide, and more than 80% of the cases occur in the developing world [2, 3].

Cervical cancer ranked as the 15th most common cancer among Jordanian women and the 10th among women between 15-44 years of age. It represents 1.6% of all female cancers registered in Jordan with an incidence rate of 3.6/100,000 women [4]. However, cervical cancer is considered to be potentially preventable [5]. It has been shown that Papanicolaou (Pap) smear [6] can reduce the mortality and morbidity of cervical cancer [7]. For this to be successful, women have to accept this test and to follow up in cases of abnormalities [7]. The incidence of cervical cancer in countries where the majority of women receive regular screening of the cervical epithelium has decreased by more

than 70% [8].

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world [9]. The prevalence of HPV infection in asymptomatic women varies between countries ranging between 2% and 44% [10]. In a report on HPV infection in the Extended Middle East and North Africa region (EMENA), Seoud highlighted the deficiencies in knowledge of HPV burden in this region and its related diseases [11]. The rapidly evolving socio-sexual behavior in this region will adversely affect current and projected HPV burden and eventually cervical cancer [12].

Unlike breast cancer screening program which was established in Jordan in 2006, cervical cancer has yet no such screening program. Among ever-married Jordanian women aged 35 or more, the life time prevalence of Pap smear was 14.3% in 2008 [13] and 27.8% in 2012 [3]. The prevalence was higher in employed women, highly educated, having high income, and covered by private health insurance [3,

13].

Cervical cancer is preceded by a group of epithelial cell abnormalities [14]. However, there is insufficient data on cervical abnormalities in Jordan and the Middle East at large [11]. According to the present authors' knowledge, the prevalence of these cytological abnormalities has never been studied in Jordan. Thus, the aim of this study was to determine the prevalence of different cytological abnormalities in women in Jordan. Also, the study aimed at analyzing the changing trends of epithelial cell abnormalities in cervical smear over a period of 15 years and assessing the age specific cytological abnormalities in these women.

Materials and Methods

A total of 6,454 conventional Pap smear tests were collected between January 2000 and December 2014 from the First Medical laboratories, Amman (the capital), Jordan. Smears were collected by obstetrics and gynecology consultants from private clinics all over Amman. The samples were evaluated by a single accredited (The American Board of Pathology) pathologist. The cytological smear results were reported according to Bethesda classification system. The results were reported as "adequate for evaluation" or "inadequate for evaluation". Adequate results were subdivided into normal, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesions (LSILs), including changes induced by HPV infection, high-grade squamous intraepithelial lesions (HSILs), and carcinoma. The cytological smear results were retrospectively analyzed.

This study was approved by the Institute Review Board (IRB) of Ibn Al-Haytham Hospital and registered with Scientific Research Committee, Faculty of Medicine, University of Jordan, which conforms to the World Medical Association Declaration of Helsinki.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), Version 20.0. Descriptive statistics were presented as numbers, percentages, and means \pm standard deviations. The Z-test was used to test the difference in proportions and the Chi-square test was used to determine if there was any trend in the proportion of cases over the study period. The two-tailed probability value $p < 0.05$ was considered statistically significant.

Results

Between 2000 and 2014, a total of 6,454 Pap smears were performed. The results of these smears were retrospectively analyzed. The mean age \pm SD of the women included in the present study was 43.2 ± 10.9 (range: 16-87) years. Out of the 6,454 Pap smears analyzed, 5,645 (87.5%) were found adequate for reporting (Table 1).

A total number of 801 (14.2 %) cases had epithelial abnormalities. The overall distribution of the Pap screening results are presented in Table 1. A significant increase in cytological abnormalities was observed between the first period and the second and third periods ($p < 0.001$), and between the second and third periods ($p < 0.001$).

The adequate Pap smears were divided over three peri-

Table 1. — Distribution of cervical Pap smear results during three five-year periods between 2000 and 2014, n (%).

| Cytological smear result | Total 2000-2014 | Period 1 2000-2004 | Period 2 2005-2009 | Period 3 2010-2014 |
|--------------------------|-----------------|--------------------------------|-------------------------------|--------------------|
| Normal | 4,825 (85.5) | 563 (93.8) ^{a3,b3} | 2,341 (87.9) ^{c3} | 1,921 (80.6) |
| ASCUS | 204 (3.6) | 4 (0.6) ^{a3,b3} | 98 (3.7) | 102 (4.2) |
| AGUS | 90 (1.6) | 11 (1.8) | 29 (1.1) ^{c2} | 50 (2.1) |
| LSIL | 463 (8.2) | 16 (2.7) ^{a2,b3} | 153 (5.7) ^{c3} | 294 (12.3) |
| HSIL | 42 (0.7) | 4 (0.7) | 30 (1.1) ^{c2} | 8 (0.3) |
| Carcinoma | 2 (0.04) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Others | 19 (0.3) | 2 (0.3) | 12 (0.5) | 5 (0.2) |
| Total | 5,645 | 600 | 2,663 | 2,282 |

a2: $p < 0.01$, a3: $p < 0.001$ period 1 vs. period 2;

b3: $p < 0.001$ period 1 vs. period 3;

c2: $p < 0.01$, c3: $p < 0.001$ period 2 vs. period 3.

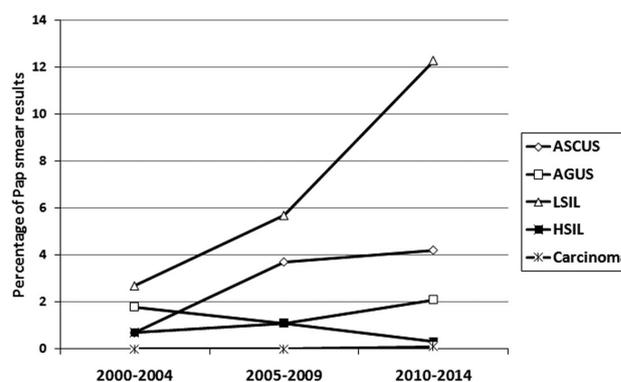


Figure 1. — Trends in cervical cytological abnormalities in Jordan between 2000-2014 (n = 5,645).

ods, five years each, and the changing trends of cervical epithelium abnormalities over the three periods were compared (Table 1). A significant increasing trend in ASCUS cases was observed between the first period and the second and third periods ($p < 0.001$) (Table 1, Figure 1). The incidence of ASCUS was 0.6% in the first period compared to 3.7% and 4.2% for the second and third periods, respectively. In the present study, ASCUS was highest in women younger than 25 years and lowest after the age of 45 (Table 2, Figure 2).

Another significant increasing trend was noted in AGUS cases between the second period and the third periods ($p < 0.001$) (Table 1, Figure 1). The rate of LSIL over the study period was 8.2% with a significant increase over time. LSIL increased from 2.7% in the first period (years 2000-2004)

Table 2. — Age specific cervical cytological abnormalities, n (%).

| Cytological smear result | Total | <25 years | 25-35 years | 36-45 years | >45 years |
|--------------------------|-----------------|-----------------------------|----------------------------|-----------------|-----------------|
| Normal | 3,994 (85.6) | 126 (79.9) ^{ab} | 912 (85.2) | 1,389 (85.8) | 1,567 (86.2) |
| ASCUS | 157 (3.4) | 7 (4.4) | 35 (3.3) | 60 (3.7) | 55 (3.0) |
| AGUS | 79 (1.7) | 3 (1.9) | 11 (1.0) ^c | 27 (1.7) | 38 (2.1) |
| LSIL | 383 (8.2) | 21 (13.3) ^{ab2} | 106 (9.9) ^{c2} | 126 (7.7) | 130 (7.2) |
| HSIL | 35 (0.8) | 1 (0.6) | 5 (0.5) | 11 (0.8) | 18 (1.0) |
| Carcinoma | 2 (0.04) | 0 (0.0) | 0 (0.0) | 1 (0.06) | 1 (0.05) |
| Others | 16 (0.3) | 0 (0.0) | 2 (0.2) | 5 (0.3) | 9 (0.5) |
| Total | 4,666 | 158 | 1,071 | 1,619 | 1,818 |

a: $p < 0.05$ age group 1 vs. age group 3;

b: $p < 0.05$, b2: $p < 0.01$ age group 1 vs. age group 4;

c: $p < 0.05$, c2: $p < 0.01$ age group 2 vs. age group 4.

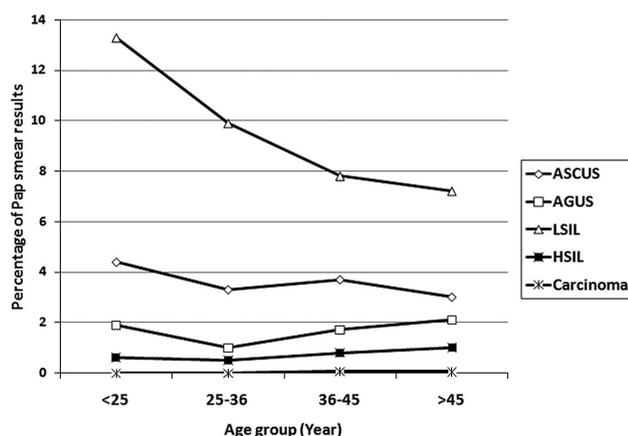


Figure 2. — Trends in cervical cytological abnormalities in Jordan by age group between January 2000 and December 2014 (n = 4,666).

to 12.3 % in the third period (years 2010-2014) (Table 1, Figure 1). However, HSIL cases showed a significant decreasing trend between the second and third periods ($p < 0.01$) (Table 1, Figure 1). In addition, the women participating in this study were divided into four-age groups (Table 2). In 979 (17.3%) of the cases, the information regarding women's age was missing. The highest percentage of cytological abnormalities was found in women younger than 25 years old (20.1%) (Table 2). In all of the age groups, the LSIL cytological abnormality was the most prevalent (Table 2), but its prevalence decreased with age (Table 2, Figure 2). Cases with ASCUS or HSIL cytological abnormality did not show any significant dif-

ference among the four age groups (Table 2, Figure 2). LSIL was highest in women younger than 25 years old (13.3 %) (Table 2) and dropped with increasing age, reaching its lowest value above the age of 45 (0.7%) ($p < 0.001$). The rate of AGUS increased significantly between periods two and period three ($p < 0.001$).

Discussion

In the current study, Pap smear results were obtained over the last 15 years and 12.5% of these cervical smears were found to be inadequate for evaluation. Worldwide, the percentage of inadequate smears ranges between 9% and 11% [7, 15]. There are many factors affecting the adequacy of the specimen such as poor sample collection, inflammation, obscuring the sample by red blood cells, and the use of lubricant [16]. Patients with unsatisfactory smears are more likely to have a history of abnormalities and are at increased risk of harboring preinvasive disease [16].

The proportion of inadequate smears in England was 9.7% before the use of liquid base cytology (LBC) [7]. The incidence dropped to 1.6 % after LBC [17]. LBC might be able to reduce the percentage of inadequate smears in women under the age of 40 [18]. Most laboratories in Jordan still use the conventional smear method. The percentage of inadequate smears in the present study (12.5%) highlights the need to shift to LBC, as it is more efficient and cost effective.

Despite the fact that cervical cancer incidence and mortality are declining in developed countries, the rate in developing countries is on the increase except in the Middle East region [11]. However, there is insufficient data on the prevalence of cervical abnormalities in this region. In the current study, it was found that 14.2 % of the cases had epithelial abnormalities and that there has been a significant increase in the incidence of abnormal smears in Jordan over the last 15 years.

The incidence of ASCUS was 0.6% in the first period compared to 3.7% and 4.2% for the second and third periods, respectively. Al Zaabi *et al.* reported an incidence of 2.5% of ASCUS in cervical screening program for the year 2013 in Abu Dhabi area/United Arab Emirates. This reflects the difference between opportunistic screening and population-based screening [19]. Vaccination was established in Abu Dhabi in 2008 [19]. In the present study, ASCUS was highest in women younger than 25 years and lowest after the age of 45.

The rate of LSIL (an indicator of HPV infection) over the study period was 8.2% with a significant increase over time. The incidence of LSIL ranged between 1.0% in Kuwait and 1.6% in Abu Dhabi [19,20]. The high rate of LSIL in the present study might be explained by the fact that these women were coming with a gynecological problem and not through a screening program. It is expected that the rate of LSIL will be much lower if a screening pro-

gram was offered for the general population. Only 27.8% of Jordanian women had ever had a Pap smear [21] and only 7.5% had a smear within the last three years [13]. Around 70% of Jordanian women had never heard of Pap smear [13, 22].

LSIL was highest in women younger than 25 years old (13.3 %) and dropped with increasing age, reflecting the peak of HPV infection in the younger age group. The rate of AGUS increased significantly between periods two and three ($p < 0.001$). The number of screened women quadrupled in the second and third periods compared with the first period. This might reflect a better awareness toward screening which is being spread, although much more still needs to be done.

The current study is a benchmark for medical professionals and policy makers in the region. It highlights the importance of initiating a cervical screening program in Jordan. An increase in abnormal smears precedes the increase in the incidence of cervical cancer. The incidence of invasive cervical carcinoma has fallen more than 70% in countries where the majority of women have regular Pap smears [8], while in the developing countries its incidence has risen significantly over the last decade. It is time for healthcare providers in the region to plan and implement a screening program.

Primary HPV screening is likely to overcome problems of sampling issues of cervical cytology as HPV DNA is more sensitive in detecting glandular lesion and less affected by transformation zone sampling [23-25]. With advancing technology, the present authors hope that cervical screening with HPV testing will be more cost effective compared with conventional screening, especially for countries with no established services for a cervical screening program.

The major limitation in the current study was the fact that it was based on opportunistic cervical screening rather than population-based. This might explain the percentage of cervical cytological abnormalities (14.2%) in Jordanian women which is higher than the surrounding countries. Another limitation was the percentage of inadequate results (12.5%) which is due to the fact that most laboratories in Jordan still use the conventional smear method rather than LBC. The current study fell short in finding the correlation between Jordan open borders and globalization and the high percentage of cytological abnormalities found.

Conclusions

People in the Middle East have a conservative sexual behavior due to religious and cultural factors. The present study may reflect a change in the sociosexual behavior over the last 15 years coinciding with the wide spread of Internet usage and social media sites [26]. It is well known that an increase in HPV infection precedes the increase in cervical cancer incidence [27]. Invasive cervi-

cal cancer is still a killer for young women in developing countries. The current work highlights the importance of awareness campaigns on the importance of cervical smear and the urgent need for initiating a cervical screening program in Jordan.

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Corresponding Author:
M.A. FREIJ, M.D., MRCOG, FICRS
Department of Obstetrics and Gynecology
Faculty of Medicine, University of Jordan
Queen Rania Street
Amman 11942 (Jordan)
e-mail: Mazen2k@yahoo.com