Cervical cancer screening with pattern of pap smear

Review of multicenter studies

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ABSTRACT

Objectives: To estimate the frequency of abnormal cervical smears and to compare the findings with earlier reported data from Saudi Arabia.

Methods: The study was divided into 2 parts. The prospective part was conducted at King Abdul-Aziz University Hospital and a private laboratory by using the Bethesda System criteria and diagnostic entities in evaluating all the pap smears that were received during the period of January 2000 to December 2004. All reliable published literature on pap smear performed at different hospitals from 1990-2004, from the Western and Abha regions of Saudi Arabia were retrospectively evaluated.

Results: A total of 5132 cases were evaluated in the prospective part of the study. The percentage of abnormal pap smears was 4.7%. The significant categories were atypical squamous cell of undetermined significance (2.4%), low grade squamous intraepithelial lesion (0.6%), high grade squamous intraepithelial lesion (0.4%) and atypical glandular cells of undetermined significance (1.1%). The malignant categories were squamous cell carcinoma (0.08%), adenocarcinoma of cervix in situ (0.02%) and invasive (0.04%). Other malignancies were 0.04% and neuroendocrine carcinoma was 0.02%. In the second part of the study, the total number of cases reported in the literature were 45596. The percentage of abnormal pap smear was1.4 %. The total cases evaluated in the current study and the previous published studies were 50,728 and the frequency of abnormal pap smear was 1.6%.

Conclusion: The percentage of abnormal pap smear was higher in the prospective part of this study than the previously reported results. Unified national programs for diagnosing cervical precancerous lesions should be established covering different region of the Kingdom to evaluate the magnitude of the problem.

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The health services providers worldwide identify the common problem affecting their society and treat it. They also work hard either to minimize the frequency of the disorder or to prevent it. Since the discovery of the effectiveness of pap smear in detecting epithelial changes in the uterine cervix prior to its progression to carcinoma of cervix, pap’s smear has been used widely as a mass screening program for women in their reproduction years to identify the precancerous lesions. Carcinoma of cervix represents a major health problem, its incidence ranking second of all cancer of the female. However, it could be prevented by early detection of its precursor. The United States Public Health Service (USPH) develop

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a panel for studying the cost effectiveness of cervical cancer screening, and one of their recommendation was to continue mass screening based on cervical cancer mortality and morbidity. In Saudi Arabia, the incidence of cervical cancer was 1.6 per year and two thirds of patients were presented with advanced disease in comparison to western countries. Although this is not high incidence in comparison with other Arab and Western countries. Yet, this cancer is preventable if a well developed mass screening programs is established to detect the premalignant lesions earlier. The health service providers in Saudi Arabia including governmental sectors and private sectors should pay more effort to evaluate the magnitude of this problem and put forward a foundation of mass screening program of cervical cancer in Saudi Arabia in order to decrease its frequency.

Methods. The study has 2 parts. The first one is a prospective study designed to estimate the frequency of abnormal pap’s smears seen in samples examined in the Department of Pathology, King Abdul-Aziz University Hospital (KAUH) and in a private laboratory (Al-Khadra Clinical Laboratories) during the period January 1999 to December 2004. The Bethesda system (TBS) criteria and diagnostic entities were used to report the smears. The major categories of epithelial cells abnormalities and its prevalence were presented in Table 1.

The second part of the study was to evaluate all previous local studies performed on cervical pap smear from 1990-2004 and tabulate their significant diagnostic categories. In one study, the number of cases overlapped were deducted from the present study since both studies were conducted at the same venue for the years 1999-2000. All diagnostic categories which were significant to identify or have a precancerous potential in this study were named: atypical squamous cell of undetermined significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), atypical glandular cells of undetermined significance (AGUS), and other atypical cells not otherwise specified. The malignant categories were squamous cell carcinoma, adenocarcinoma, and other malignancy not otherwise specified. All reactive epithelial changes and benign cellular changes due to infection and other causes were not considered as abnormal categories of any premalignant potential.

Results. The total number of pap smears evaluated in the prospective part of the study was 5132 (Table 1). The total epithelial cells abnormalities (ECA) were 243; 4.7% of the total pap’s smear seen. The highest prevalence among the abnormal epithelial cells categories being showed were ASCUS (50.2%), AGUS (23.9%), LSIL (12.75%) and HSIL (8.9%). The total number of invasive malignant pap smear was 9 cases which represent 3.7% of the epithelial cell abnormalities and represent 0.17% out of the total pap’s smears examined. The total number of uterine malignancy namely invasive squamous cell carcinoma and invasive adenocarcinoma was 6 cases which represent 2.49% of ECA (0.11% of the total pap smears studied). The total number of all previously published cases were 45596 in different hospital in Jeddah and Abha area from 1990-2004 (Table 2). Three thousand and fifty-three cases were overlapped and excluded, 84 cases were with abnormal smears. The total number of cases reported from the Western and Abha Regions of Saudi Arabia in addition to the prospective part of this study was 50728. The number of abnormal pap smears were 805 (1.58%) from the total number examined. Atypical squamous cell of undetermined significance was 286 (0.56%), LSIL 173 (0.34%), HSIL 139 (0.27%) and AGUS 135 (0.26%). The malignant cases were squamous

Table 1 - Epithelial cell abnormalities categories and percentage (prospective part of the study). The total number of cases were 5132 and total number of abnormal pap smears were 243.

<table>
<thead>
<tr>
<th>Epithelial cells</th>
<th>n</th>
<th>TAPS %</th>
<th>TSE %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Squamous cells</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCUS</td>
<td>122</td>
<td>50.2</td>
<td>2.4</td>
</tr>
<tr>
<td>LSIL</td>
<td>31</td>
<td>12.75</td>
<td>0.6</td>
</tr>
<tr>
<td>HSIL</td>
<td>22</td>
<td>9.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>179</td>
<td>73.7</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Glandular cells</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGUS</td>
<td>58</td>
<td>23.9</td>
<td>1.10</td>
</tr>
<tr>
<td>Glular Cis</td>
<td>1</td>
<td>0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Endocervical adenocarcinoma</td>
<td>2</td>
<td>0.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Endometriar adenocarcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extraterine adenocarcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>61</td>
<td>25</td>
<td>1.19</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant cell NOS</td>
<td>2</td>
<td>0.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Neuro endocrine carcinoma</td>
<td>1</td>
<td>0.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3</td>
<td>1.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>

ASCUS - atypical squamous cell of undetermined significance, LSIL - low grade squamous cell intraepithelial lesion, HSIL - high grade squamous intraepithelial lesion; CIS - carcinoma in situ, AGUS - Atypical glandular cell of undetermined significant; NOS - not otherwise specified, TAPS - percentage of total abnormal pap’s smear, TSE - percentage of total smears examined.
cell carcinoma 33 (0.07%), adenocarcinoma of cervix 5 (0.01%), endometrial carcinoma 7 (0.013%), and other malignancy 26 (0.05%).

Discussion. Fifty years ago, carcinoma of the cervix was the leading cause of death among female in the United States of America. However, recently the death rate has declined to two third.² Now it ranks number 8 in mortality, preceded by cancers of the lung, breast, colon, pancreas, ovary, lymph node and blood. The estimated cases of invasive cervical carcinoma detected annually were 13000 and the number of pre invasive lesions detected annually is one million.

Cervical cancer causing death approximately in 4500 women annually.³ The cause of this sharp contrast in death reduction is related to papanicolaou smear test in detecting cervical precancerous condition of varying grade. Therefore, pap smear screening has increased the detectability rate of a potentially curable cancer by detecting its intraepithelial precancerous lesions which some of it will progress to cancer if not treated.³ The predisposing factors of cervical carcinoma are well documented in the literature and they are the same for the precancerous lesion of the cervix. The most important predisposing factor is uncontrolled sexual intercourse. Infection by human papilloma virus (HPV) which is transmitted by sexual habit is a very strong risk factor. The uterine cervix is frequently infected by oncogenic HPV typed 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 68⁴ and non-oncogenic virus typed 6, 11, 42, 43, and 44. Both oncogenic and non-oncogenic viruses are able to cause latent and clinical infection of both squamous and glandular epithelium of the cervix. The significant cytological changes were classified as LSIL and HSIL, the latter can give rise to invasive cervical carcinoma. The cytomorphic feature of oncogenic and non-oncogenic HPV infection of cervix result in “Koilocytosis”⁵ in which the squamous cells exhibit cellular enlargement with irregularity of nuclei and hyperchromasia. The oncogenic types of HPV are viruses that integrate into the host DNA and produce E6 and E7 proteins which interferes with the cellular tumor suppressor genes Rb gene and P53 result in uncontrolled cellular proliferation and transformation. Follow-up studies of HSIL/ CIN III (cervical intraepithelial neoplasia) without intervention suggest that only 20-25% of these cases will develop invasive carcinoma of the cervix.⁶-¹² Because of lack of accurate method to detect which cases will progress to invasive carcinoma therefore over treatment of all patients at risk to develop squamous cell abnormalities. In addition, 15% of cervical cancers are not associated with HPV, leaving open to question other pathway of cancer development, including host gene mutation. Current knowledge on human cancer indicates that all malignant cells are actually monoclonal originated from a single transformed cell, whereas CIN has proven to be polyclonal with some being monoclonal.¹³ It is the monoclonal type that usually progress to invasive cancer and can be detected by genetic testing.¹⁴-¹⁵

In our society, cervical cancer rank number 10 in frequency in all female cancer in Saudi Arabia, and its prevalence is 3% preceded by breast, thyroid, leukemia, lymphoma, brain tumor, colon, oral cavity, ovary and Hodgkin lymphoma.¹⁶ The age specific rate (ASR) was 2/100,000 female population. The highest region was found in Al-Jouf comprised 3.8/100,000 followed by Riyadh region (2.8/100,100) followed by Makkah and the eastern region 2.7 each and then Qassim region 2.4/100,000. The mean age at

Table 2 - Summary review of significant precancerous and malignant lesions of previous studies.

<table>
<thead>
<tr>
<th>Author's name</th>
<th>Year Published</th>
<th>N</th>
<th>ASCUS</th>
<th>LSIL</th>
<th>HSIL</th>
<th>SCC</th>
<th>AGUS</th>
<th>Endocervical carcinoma</th>
<th>Endometrial carcinoma</th>
<th>Malignant NOS</th>
<th>Abnormal smears</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abduljabbar⁴</td>
<td>1990</td>
<td>21372</td>
<td>NA</td>
<td>24</td>
<td>27</td>
<td>-</td>
<td>NA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>51</td>
<td>0.2</td>
</tr>
<tr>
<td>Altaf²</td>
<td>2001</td>
<td>3088</td>
<td>14</td>
<td>29</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>69*</td>
<td>2.2</td>
</tr>
<tr>
<td>Jamal et al²</td>
<td>2003</td>
<td>22089</td>
<td>111</td>
<td>81</td>
<td>72</td>
<td>26</td>
<td>36</td>
<td>7</td>
<td>5</td>
<td>22</td>
<td>360†</td>
<td>1.6</td>
</tr>
<tr>
<td>El-Hakeem et al⁶</td>
<td>2004</td>
<td>2100</td>
<td>58</td>
<td>27</td>
<td>14</td>
<td>7</td>
<td>54</td>
<td>-</td>
<td>2</td>
<td>4*</td>
<td>166</td>
<td>7.9</td>
</tr>
<tr>
<td>Overlapped cases</td>
<td>1999-2000</td>
<td>3053</td>
<td>19</td>
<td>19</td>
<td>13</td>
<td>8</td>
<td>17</td>
<td>5</td>
<td>-</td>
<td>3</td>
<td>84</td>
<td>2.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>45596</td>
<td>164</td>
<td>142</td>
<td>117</td>
<td>29</td>
<td>77</td>
<td>3</td>
<td>7</td>
<td>23</td>
<td>562</td>
<td>1.4</td>
</tr>
</tbody>
</table>

⁶9* represent the real abnormal pap's smears that has pre-malignant cellular abnormalities after the exclusion of benign cellular changes. 360† represent the real abnormal pap's smear that carry the pre-malignant and malignant cellular changes after the exclusion of benign cellular changes. 4* - ASCUS/HSIL cannot be excluded. LSIL - low grade squamous cell intraepithelial lesion, HSIL - high grade squamous intraepithelial lesion; SCC - squamous cell carcinoma, ASCUS - atypical squamous cell of undetermined significance, AGUS - Atypical glandular cell of undetermined significant, NOS - not otherwise specified, NA - not available.
Cervical cancer screening with pattern of pap smear ... Altaf

diagnosis was 51 years; however the 2 peak ages were 40 years and 55-65 years. If cervical cancer pathogenesis was identified in Western countries applied to our society, we may suggest that Saudi’s have a lower rate of HPV infection since we have lower rate of cervical carcinoma. On the other hand, the precancerous lesions in our society are lower in frequency compared to western society. This conclusion is difficult to draw since no cervical cancer screening program is present in Saudi Arabia and all data in our population were collected from hospital based studies; hence, the majority of the patients were seen in gynecological clinics or post partum. Therefore, information is not available on the rest of asymptomatic females. Data obtained from cervical cancer screening program are very strong to determine the real magnitude of this problem. If we look at the major reliable studies carried out in Saudi Arabia including the current study, and analyze the data, it appears that approximately more than 50 thousands cases were evaluated in Jeddah and Abha regions. The percentage of abnormal pap’s smear was approximately 1.6%, which is much lower than the western society. If we compare our findings to a low incidence population of HPV infection such as North Vietnamese in Hong Kong detention center, we have a higher incidence of abnormal pap smear (1.6% versus 0.8%). Our LSIL was comparable (0.3% versus 0.2%) while our HSIL was lower (0.3% versus 0.5%), and the other abnormal categories account for the difference in the frequency. In the previous study, the cases have a low incidence of risk factors for cervical cancer compare to the Western society, such as number of sexual partners and early age of sexual activity (<16 years) (14%), had only one partner, and had their first sexual intercourse after age of 20 (78%). Another low incidence of HPV infection and its related lesions such as ASCUS (0.05%), LSIL (0.92%), HSIL (1.52%), AGUS (0.025%) were seen in Czech Republic; and the incidence of carcinoma of the cervix was lower (0.2%). Literature reports from other Arab countries places cervical cancer as the third most common cancer in Kuwait with incidence of 7.6 per 100,000 populations, preceded by breast and lung. The higher incidence in Kuwait could be related to the preparation methods used to study cervical precancerous lesion which was thin preparation pap’s test. This study findings indicate that Saudi Arabia had a lower frequency of cervical disease, which could be related to the Islamic rules in controlling sexual relationship, or it could be related to other environmental or genetic factors that need further investigations. If one consider cervical cancer screening program in Saudi Arabia the cost effectiveness of this program should be established by integrating several sources of data including solid information on incidence and etiology of cervical cancer from large epidemiological studies if available, or Health Care Providers should sponsor large scale studies to identify the etiology of cervical cancer. Clinical trials and observational data on the cost and health benefits of different methods of preventing, treating or palliating cervical cancer should be integrated. Studies conducted so far in Saudi Arabia were localized to certain areas, and might not reflect true national incidence. Therefore, the incidence of premalignant epithelial lesions of the cervix has to be estimated based from official National Resources. Furthermore, cervical cytology guidelines have to be established before any large national screening program is started. The objective of the screening program must be very clear, and should include the estimate of the incidence of cervical cancer and its precancerous lesion and to reveal the real magnitude of this problem. The result of such national screening might justify cost effectiveness of further continuous national mass screening program for cervical cancer. Documentation of risk factors such as human papilloma virus (HPV) and its subtype has to be identified by pap smear and confirmed by molecular methods such as polymerase chain reaction (PCR) or hybrid capture assay (HCA). Proper specimen collection and submission is essential to identify in order to avoid false negative results. Using the provided cytopathology examination and reporting form of the cervix will be of help. Protocol for visualization and collection devices to insure adequate sample is important to establish before starting screening as well as proper labeling of the sample and methods of handling is recommended to specify. Liquid based preparation or thin prep pap’s test is superior to conventional pap’s smear preparation with high diagnostic accuracy over conventional smear. The methods of reporting should be unified and similar terminology is applied. The Bethesda system (TBS) for reporting pap’s smear is highly recommended. Patient follow-up protocol should be applied clearly as well as treatment policies. Quality control and quality assurance methods should be established and followed.

In conclusion, abnormal cervical lesions are important to identify in order to reduce the incidence of cervical cancer. However, the real need for mass screening program in Saudi Arabia cannot be decided

*The full text including Appendix is available in PDF format on Saudi Medical Journal website (www.smj.org.sa)
unless strong data is collected from pilot studies in different regions of Saudi Arabia sponsored by Heath Service Providers, and the recommendations of these studies will determine the necessity of continuous mass screening program.

References


### APPENDIX: CYTOPATHOLOGICAL EXAMINATION AND REPORTING OF THE CERVIX

| Registration number | Date of smear  _____/_____/_____
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of patient</td>
<td>Years of marriage  :</td>
</tr>
<tr>
<td>Name of husband</td>
<td>Widow              :</td>
</tr>
<tr>
<td>Place of birth</td>
<td>Tel. / Fax #       :</td>
</tr>
<tr>
<td>Native country</td>
<td>Citizenship        :</td>
</tr>
<tr>
<td>Residence</td>
<td>:</td>
</tr>
<tr>
<td>Insurance company</td>
<td>:</td>
</tr>
<tr>
<td>Lab number:</td>
<td></td>
</tr>
<tr>
<td>Date of receipt:</td>
<td></td>
</tr>
<tr>
<td>Hospital number:</td>
<td></td>
</tr>
</tbody>
</table>

#### Personal data

1. Indication of smear
   - Initial screening
   - Repeat after inadequate
   - Follow-up

5. Personal data
   - Smoking
   - Sexual activity
     - Active
     - Inactive

9. Use of hormone
   (otherwise than contraceptive)
     - No
     - Yes
     - Unknown

2. Smear by
   - Family doctor
   - Gynecologist
   - Otherwise _______________

6. Date of menstruation _____/_____/_____

10. Pregnancy
    - Pregnancy - weeks
    - Post partum - weeks
    - Lactation - weeks
    - Post lactation - weeks

3. Instrument smear
   - Cervix brush
   - Cytobrush and spatula
   - Spatula
   - Otherwise _______________

7. Menstruation pattern
   - None
   - Regular
   - Irregular
   - Post-menopausal (>1 yr. no menstruation)
     - Otherwise _______________
     - Unknown

4. Complaints
   - None
   - Vaginal bleeding
   - Vaginal discharge
   - Cervicitis
   - Post-coital discharge

8. Contraceptive
   - Unknown
   - Hormonal
   - IUCD
   - Otherwise _______________

11. Cervix
    - Normal
    - Not seen
    - Abnormal/suspect portio
      - ASCUS
      - ASCUS-H
      - LSIL
      - HSIL
      - AGUS
      - CIS
      - Endocervical ca
      - Endometrial ca
    - Other malignancy
      - Infection
        - Non-specific
        - Candida
        - Trichomonas
        - Other specific
    - Other abnormalities

13. Surgery of the cervix
    - No
    - Cryo, or laser
    - Conisation, leep excision, biopsy
    - Supravaginal uterus extirpation
    - Radiotherapy
    - Combination
    - Otherwise _______________
    - Unknown

12. Cytology
    * WNL
      - Satisfactory
      - Unsatisfactory
      - Sq. <10%
      - Obscuring blood
      - Obscuring inflammation
      - Others

14. HPV typing
    - Low risk virus
    - High risk virus

15. Remarks
    - Normal
    - Yes: _____

16. Recommendation
    - Treat inflammation and repeat
    - Repeat after 6-8 mos.
    - Repeat after 5 yrs.
    - Otherwise _______________

WNL - within normal limits