Randomly Selected Smear Test Screening Outcome

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Background: The cervical cancer screening coverage in Bahrain was 43.1% in 2018. Even with the presence of a screening program, most screening in the Middle East usually take place at random.

Objective: To evaluate the risk factors and outcome of randomly selected smear tests.

Design: A Retrospective Study.

Setting: Bahrain Defence Force Hospital, Bahrain.

Method: All Pap smear tests performed from January 2017 to December 2017 were included in the study. The smear results were divided into four groups: normal, borderline, premalignant changes and malignant changes. Risk factors such as age, parity, contraceptive/medical history, smoking, and human papillomavirus (HPV) positive screening were documented. The outcome of care were divided into four categories: repeat smear test, colposcopy and cervical biopsy, hysteroscopy/dilatation and curettage, and hysterectomy.

Result: A total of 2,626 smear tests were included in the study; 2,246 (85.5%) were negative smears. Two hundred forty (9%) were borderline and 135 (5%) had pre-cancerous lesions. Five (0.2%) cases were malignant; the older the patient, the higher the risk of malignant changes. Twenty-nine (1.1%) of the previous pre-cancerous smear became negative on the successive smear and 72 (2.7%) patients had repeat smear test. Some of the negative and borderline patients had a hysterectomy.

Conclusion: A uniform cervical screening policy must be initiated and cost-effective clear protocols must be laid down to improve the quality of women's health in Bahrain.

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Cervical cancer is the second most common cancer in women worldwide, although it is a theoretically preventable disease[1]. The causal role of human papillomavirus infections in cervical cancer has been proven[1]. The addition of a HPV test to the Pap test to screen women in their mid-30's for cervical cancer reduces the incidence of grade 2 or 3 cervical intraepithelial neoplasia (CIN) or cancer detected by subsequent screening examinations[2,3,4,5]. Non-randomized studies indicate that HPV testing is more sensitive than a Pap smear for identifying cervical cancer and its precursors in population screening[6]. HPV tests are less likely to miss CIN2 and CIN3. However, they do lead to unnecessary referrals. A negative HPV test is more reassuring than a negative cytological test[7]. A recent study highlighted the importance of screening efforts and expanding existing cancer control efforts with HPV vaccinations[8].

In the developing world, there are still countries that fail to provide access to cytology-based screening activities as well as treatment of precancerous lesions[9]. The National Health Service (NHS) cervical cancer screening program screen at different intervals depending on a woman's age[10]. The impact of NHS cervical screening program is immense. Since its introduction, it has been estimated to have saved approximately 4,500 lives per year in England[11].

Cervical cancer trends vary in each country depending on effective screening programs and risk factors[8]. In Bahrain, approximately 19 new cervical cancer cases are diagnosed annually; cervical cancer ranks as the eighth leading cause of female cancer in Bahrain and is the 5th most common female cancer in women aged 15 to 44 years[12]. Approximately 12 cervical cancer deaths occur annually. Cervical cancer ranks 6th leading cause of female cancer deaths. The cervical cancer screening program coverage in Bahrain was 43.1% in 2018. It included all women aged 30-65 years screened every 5 years. Individuals are screened annually for 3 years and if there are 3 consecutive negative smears, they are then screened every 3 years[12]. The HPV vaccine program is not available in Bahrain. Even with the presence of a screening program, most screening in the Middle East usually take place at random and based on the clinical situation.

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The aim of this study is to evaluate the risk factors and outcomes of randomly selected smear test.

METHOD

All Pap-smear tests (2,626 cases) performed from January 2017 to December 2017 were included in the study. The smear test is usually performed during the postnatal checkup or if the patient presents with symptoms such as abnormal uterine bleeding. All cases with missing data were excluded. The smear result was divided into four groups. Group 1 was normal smears; it included other reported results such as candida, bacterial vaginosis, endometrial cells, follicular cervicitis, herpes simplex virus, trichomoniasis, benign cervical polyp, disordered proliferative endometrium and actinomyces. Group 2 was borderline smears; it included smears with atrophic cervicitis, borderline nuclear changes and unsatisfactory smears. Group 3 included the pre-malignant changes which comprise atypical endometrial cells, atypical glandular cells, atypical endocervical cells, atypical squamous cells, CGIN-1 focal, mild dyskaryosis, moderate and high-grade dyskaryosis. Group 4 included the malignant changes which included adenocarcinoma cells and cancer of the endometrium.

Risk factors such as age, parity, oral contraceptive use, intrauterine contraceptive device (IUCD), injectable contraception/Depo Medroxyprogesterone Acetate (DMPA), smoking and HPV positive screening were documented. Other factors which increase the risk of abnormal smears such as infertility, polycystic disease, hypothyroidism, diabetes mellitus and previous history of any other malignancies were documented. The outcomes were divided into four categories. Action 1 was to repeat the smear test on variable intervals between 6 months and 3 years. Action 2 was colposcopy and cervical biopsy, cervical diathermy and large loop excision of the transformation zone. Action 3 was hysteroscopy and dilatation and curettage. Action 4 was hysterectomy which included abdominal, vaginal and laparoscopic approach.

Data were analyzed using StatsDirect statistical package version 3.1.22 (2018 Cambridge, UK). One-way analysis of variance was used to compare the mean age among the groups. Kruskal-Wallis test was used to compare medians of parity between the study groups. Fisher- Freeman-Halton exact in crosstabs was used to compare the percentage of different contraceptive usage, previous medical history, HPV positive patients, previous smear result and action plan. P-values of less than 0.05 were considered statistically significant.

RESULT

A total of 2,626 smear tests were included in the study; 2,246 patients were negative with an incidence of 85.5%. Two hundred forty (9%) cases were reported as borderline and 135 (5%) cases had pre-cancerous lesions. Five (0.2%) cases were reported as malignant. The malignant smear results were found in patients with a mean age of 56.4 years compared to a mean age of 40.4 years in the pre-cancerous lesions. Borderline nuclear changes were found in patients with a mean age of 39.7 years and negative smears were found in patients with a mean age of 37.7 years (P-value < 0.0001). No difference was found in the number of previous deliveries among the smear test groups. We found high IUCD users and HPV -positive individuals in the pre-malignant smear group with P-value of 0.02 and < 0.0001, respectively. There was no significant difference in OCP usage and injectable contraceptives in the smear test groups. None of the malignant smears had HPV + results. We found a higher incidence of smoking in the borderline smear group, 2 (0.07%) but it did not reach statistical significance, see table 1.

Table 1: Risk Factors

	Negative (2,246) N (%)	Borderline (240) N (%)	Pre-CA (135) N (%)	Malignant (5) N (%)	P-value
Age mean ± SD	37.7±11.6	39.7±10.9	40.4±12.3	56.4±13.2	<0.0001*
Parity median (range)	3 (15-0)	3 (11-0)	3 (14-0)	4 (7-0)	0.29**
OCP	136 (5.1%)	18 (0.6%)	10 (0.4%)	0 (0)	0.65***
IUCD	65 (2.5%)	9 (0.3%)	11 (0.4%)	0 (0)	0.02***
Injectable contraceptive	23 (0.9%)	2 (0.07%)	0 (0)	0 (0)	0.75***
HPV positive	3 (0.1%)	11 (0.4%)	29 (1.1%)	0 (0)	<0.0001***
Smoking	8 (0.3%)	2 (0.07%)	0 (0)	0 (0)	0.32***

*One-way analysis of variance **Kruskal-Wallis test ***Fisher-Freeman-Halton exact

Patients with a smear test positive for malignancy had a higher incidence rate of a positive previous medical condition, but this difference did not reach statistical significance (P=0.05). However, we found a higher incidence rate of diabetic patients in the malignant group (P=0.009). There was no significant difference in the presence of a history of infertility, polycystic ovarian syndrome, hypothyroidism and previous history of any other malignancy between the smear test groups, see table 2.

Table 2: Medical History

	Negative (2246) N (%)	Borderline (240) N (%)	Pre-CA (135) N (%)	Malignant (5) N (%)	P-value
History of infertility	181 (6.8%)	21 (0.8%)	5 (0.1%)	1 (0.03%)	0.14***
Positive medical history	232 (8.8%)	33 (1.2%)	22 (0.8%)	1 (0.03%)	0.05***
PCO	21 (0.8%)	2 (0.07%)	0 (0)	0 (0)	0.81***
Hypothyroid	7 (0.3%)	0 (0)	1 (0.03%)	0 (0)	0.47***
DM	183 (6.9%)	27 (1%)	21(0.8%)	1 (0.03%)	0.009***
History of cancer	9 (0.3%)	2 (0.07%)	0 (0)	0 (0)	0.36***

*** Fisher-Freeman-Halton exact

Two thousand sixty-five (78.6%) previously negative smears continued to be negative. One hundred seventy-one (6.5%) borderline cases previously had negative smears. Eighty-seven (3.3%) pre-malignant cases previously had negative smears. Five (0.2%) malignant cases had previously negative smears. One hundred fifty-one (5.7%) previously borderline cases became negative after repeat smear. Sixty-four (2.4%) of the smears which showed borderline nuclear changes persisted in the repeat smear. Thirteen (0.5%) previously borderline cases had a pre-cancerous change in the successive smear. Twenty-nine (1.1%) previous pre-cancerous smears became negative. One (0.03%) case of previously malignant smear had

a negative repeat smear. All patients with malignant lesions had a hysterectomy or hysteroscopy/dilatation or curettage. Two hundred-eight (7.9%) cases of borderline nuclear changes had a repeat smear; 19 (0.7%) cases had a colposcopy and cervical biopsy. Nine (0.3%) borderline nuclear changes underwent a hysterectomy. Fifty-one (1.9%) pre-cancerous smears underwent colposcopy procedure and the rest had a hysterectomy or hysteroscopy/dilatation and curettage. The majority of the negative smear group had a repeat smear test. Six (0.2%) cases with negative smear underwent colposcopy and cervical biopsy. Thirty-five (1.3%) negative smear group underwent a hysterectomy, see table 3.

Table 3: Smear Test Outcome of Care

	Negative 2,246 (85.5%)	Borderline 240 (9.1%)	Pre-CA 135 (5%)	Malignant 5 (0.2%)	P-value
Previous negative	2,065 (78.6%)	171 (6.5%)	87 (3.3%)	5 (0.2%)	<0.0001***
Previous borderline	151 (5.8%)	64 (2.4%)	13 (0.5%)	0 (0)	
Previous pre- CA	29 (1.1%)	5 (0.2%)	35 (1.3%)	0 (0)	
Previous malignant cells	1 (0.03%)	0 (0)	0 (0)	0 (0)	
Repeat smear	2,196 (83.6%)	208 (7.9%)	72 (2.7%)	0 (0)	<0.0001***
Colposcopy/ biopsy	6 (0.2%)	19 (0.7%)	51 (1.9%)	0 (0)	
Hysterectomy	35 (1.3%)	9 (0.3%)	4 (0.2%)	4 (0.2%)	
Hysteroscopy D&C	9 (0.3%)	4 (0.2%)	8 (0.3%)	1 (0.03%)	

*** Fisher-Freeman-Halton exact

DISCUSSION

Abnormalities detected by Pap smear and HPV can be treated in the early stages. Many risk factors of cervical malignancy had been identified. Increased age is a crucial factor in cervical malignancy, as found in our study. High parity had a higher risk of CIN3/Carcinoma in situ compared to nulliparous women[13]. Our study found that increasing parity is not a risk factor for the development of cervical premalignant or malignant changes, which is dissimilar to another study that linked high parity to an increasing risk of squamous cell carcinoma of the cervix among HPV women[14]. In our study, HPV was positive in 21% of the premalignant smears compared to another study which found that HPV has a role in cervical cancer[15].

Brinton et al suggested that reproductive factors are cervical cancer risks[16]. Luhn et al, found that long-term oral contraceptive use (more than 10 years) was a risk factor[17]. However, our study did not show any effect relating to contraceptive use. In our study, the premalignant smear had a significantly higher incidence of (IUCD) users. Castellsague et al found that (IUCD) usage may be a protective cofactor in cervical carcinogenesis; they attributed their findings to possible cellular immunity[18]. Injectable contraceptives have been considered as a risk factor for malignancy. The WHO collaborative study of neoplasia and steroid contraceptives showed a relative risk of 1.2 for invasive cancer in the long-term progestational contraceptives (DMPA). Furthermore, an estimated relative risk of 2.4 was reported in those using contraceptives for more than 5 years[19]. Our study did not reveal an increase in the injectable contraceptives users in the premalignant or malignant groups.

An association between diabetes mellitus and cervical malignancy changes was identified in our study. Similarly, one study found that diabetes mellitus is a risk factor for cancer of the uterine corpus, vulva and vagina[20]. There was no mention of any association with cancer of the cervix. In our study, smoking did not play a role in premalignant and malignant smears. Studies showed that passive smoking was linked to an increased risk of cervical cancer[21].

Our study revealed that all the malignant smears had previous normal smears; this could be a false negative finding. Studies have shown that 100% Rapid Review is an effective screening tool for false-negative results in countries where HPV DNA testing and prophylactic vaccines are not available[22]. A study found a significant association between cytology diagnosis and progression of cervical abnormalities; women diagnosed with atypical glandular cells had a higher risk of progression of cervical abnormalities compared to women with atypical squamous cells[23]. In our study, all patients who were identified with atypical glandular cells were subjected to hysteroscopy and dilatation/curettage.

One of the limitations to our study was the retrospective nature. Files with missing variables were excluded. Furthermore, upon reviewing the cases, some of the included cervical smear tests were vault smear performed after completing treatment for malignancy. In this study, some patients opted for hysterectomy rather than colposcopy for unrelated causes, such as bleeding history or history of breast cancer with thick endometrium.

CONCLUSION

A uniform screening policy must be initiated and cost-effective clear protocols must be laid down to improve the quality of women's health.

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