



Research Article

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## Cross-sectional Multicenter Study of Pre-Cancerous Lesions and Cervical Cancer in the Eastern Province of Saudi Arabia.

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**Abstract**

**Background and Aim:** Cervical cancer and its precursors (cervical intraepithelial neoplasia) are common in women world-wide. The status in Saudi Arabia is understudied. The aim of this study is to determine the prevalence of pre-cancerous lesions of the cervix and cervical cancer of patients in Eastern Province of Saudi Arabia.

**Methods:** This is a multicenter retrospective cross-sectional study conducted on patients aged between 21-65 years with precancerous lesion of cervix and cervical cancer admitted in three hospitals in the Eastern Province on a 10-year period (2009-2019).

**Results:** A total of 363 patients (264 pre-cancerous lesions and 99 cervical cancer) were included. The mean age was  $45.95 \pm 10.12$  years. Those with pre-cancer lesion were more likely to smoke with an OR of  $2.25(1.002-5.06)$ . Similarly, pre-cancerous lesion patients had higher consumption of Oral Contraceptives  $OR=1.23(0.72-2.11)$ . The rate of intervention was the highest in colposcopy followed

by surgery, chemo radiation, and chemotherapy, respectively. The overall death rate was 20.1% which was significantly higher in Patients with Cervical Cancer.

**Conclusion:** This study showed smoking and oral contraceptive use posed a great risk to development of the disease. In addition, pre-cancerous cervical lesions and cervical cancer have many co-factors, among which are human papillomavirus (HPV), herpes simplex virus and HIV infection, moreover lack of screening programs, lack of awareness of the disease in Saudi Arabia . This study can act as an anchoring point on guiding national screening programs in the future in Saudi Arabia.

**Keywords:** Cervical Cancer; Precancer Lesion; Screening; HPV; Saudi Arabia

**Introduction**

Cervical cancer is the second most prevalent cancer among women worldwide, especially in the age group of 20-40 years, with an expected 604,127 new cases and 341,831 deaths reported [Sung et al 2021]. Cervical cancer remains the second highest cause of cancer-related deaths after breast cancer, accounting for almost 10% of cancer-related deaths [AlHarfi et al 2019; Sung et al 2021]. About 241 new cervical cancer cases were diagnosed annually in Saudi Arabia (estimation for 2012). Cervical cancer ranks as the 8th leading cause of female cancer in Saudi Arabia, affecting women aged 15-44 years in particular [ICO/IACR 2016].

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According to the Saudi Ministry of Health's 2014 estimation, the numbers of new cervical cancer cases and deaths by the year 2025 would be 309 and 117, respectively. Thus, screening and treatment of pre-cancerous lesions may be beneficial for preventing cervical cancer since detecting early cases of suspicious cervical lesions cancer can enhance patients' likelihood of survival outcomes and better quality-of-life [Sagr et al 2014].

The prevalence of cervical cancer and pre-cancerous lesions are unknown in the Eastern Province of the Kingdom of Saudi Arabia. Currently, the main public health data and statistics provides data of cervical cancer patients from the Saudi Cancer Registry office which covers the entire country. This general data, by definition, is not comprehensive enough in providing the information required for developing a better understanding of the disease, pathology, clinical presentation, survival outcomes, and types of therapy received by the patients in the Eastern Province of the Kingdom.

Similar to the global trend, the most common form of cervical cancer in Saudi Arabia is squamous cell carcinoma followed by adenosarcoma [Alsbeih et al 2011]. Around two-thirds of Saudi women diagnosed with late-stage cervical cancer are not diagnosed sooner due to the lack of proper screening programs and lack of awareness/knowledge of the availability of a vaccine [Alsbeih et al 2011; Manji 2000]. In Eastern Province of the Kingdom, we lack comprehensive database for many of gynecology oncology diseases and one of the preventable diseases is cervical cancer. Thus, in this cross-sectional study we sought to create a database that may help establish a screening program for cervical cancer in the Eastern Province like the international guidelines [Jesson 2001]. Our guiding hypothesis is that establishing a database would provide better opportunities for us to evaluate the prevalence of pre-cancerous cervical lesions and cervical cancer in the Eastern Province and that could be utilized as a tool to structure a national screening program for this preventable disease, i.e. cervical cancer.

The aim of this study is to determine the prevalence of pre-cancerous lesions of the cervix and cervical cancer of patients in eastern province of Saudi Arabia.

## **Methods and Materials**

### **Study design and Participants**

This is a multicenter retrospective cross-sectional study conducted on patients with precancerous lesion of cervix and cervical cancer diagnosed in multiple hospitals in the Eastern Province of the Kingdom [i.e., Imam Abdulrahman Bin Faisal University (IUA), King Fahad Specialist Hospital, Dammam (KFSH-D); and National Guard Hospital, Ahsa (NGH-A)] on a 10-year period (2009-2019).

### **Inclusion and Exclusion Criteria**

Patients must be aged between 21-65 years; in agreement with the international recommendations to stop taking pap smear for patients above 65-years of age unless the patient came with symptoms of cervical pre-cancerous or cancerous lesion. Cases must have been with any of the following histopathological characteristics: LSIL(Low-grade squamous intraepithelial lesion), HSIL( High- grade squamous intraepithelial lesion), AGUCS(atypical glandular cells of undetermined significance) , and any types of invasive cervical cancers (squamous cell carcinoma and adenosarcoma,etc.) . We excluded patients with ASCUS (atypical squamous cells of undetermined significant) histopathology,since the risk of cancer is less than 1% . Data collection

Patients' identification was handled through the respective hospital's cancer registry by the patients' national identification or Iqama, which were kept confidential and only accessed by the principal investigator of the study. Information regarding therapy, surgery, and pathology, were managed through the MedicaPlus and Impax clients and chart reviews if they were referred to the primary institution i.e., KFSH-D. Occasionally, phone communication was required to gain additional information/data from patients who have shown no referral and/or follow-up with the KFSH-D during a reasonable period. No direct recruitment of subjects was applied for this study.

### **Ethical Considerations**

The study was approved by IRB committee. Due to the retrospective nature of the study, informed consent from the participating individuals was not required by the ethical review board. This research received no specific grant from any funding agency in public, commercial, or nonprofit sectors.

### **Statistical analysis**

Reports were collected then coded and revised, and data was introduced on statistical software IBM SPSS version 18.0. All statistical analysis was done using two-tailed tests and an alpha error of 0.05. A P-value less than 0.05 was considered to be statistically significant. Frequencies and percentages were used to describe categorical variables whereas means and standard deviation were used for continuous variables. Pearson Chi-square was used to evaluate the relationships between different groups and dichotomous and multinomial variables respectively (Fisher's exact was used when conditions are not fulfilled). Independent T test was used to evaluate the difference between means of distinct groups of patients.

## Results

A total of 363 patients [pre-cancerous lesions (n=264) and cervical cancer (n=99) cases] formed the basis of our dataset and analyses. Table 1 shows that the prevalence of precancerous lesion of cervix is 0.023% and 0.0088% for cervical cancer during study period (from 2009 to 2019).

Year	Total	Patients with Pre-Cancerous Lesions		Patients with Cervical Cancer	
		Number of Cases	Prevalence (percentage)	Number of Cases	Prevalence (percentage)
2009	994308	4	0.00040229	1	0.000100572
2010	1017161	10	0.000983129	6	0.000589877
2011	1041747	25	0.002399815	8	0.000767941
2012	1066386	20	0.001875493	8	0.000750197
2013	1093255	32	0.002927039	3	0.00027441
2014	1120086	41	0.003660433	11	0.000982067
2015	1146009	31	0.00270504	10	0.000872593

**Table 1:** Prevalence of precancerous lesions of cervix and cervical cancer in the Eastern Province of the Kingdom (2009-2019).

Table 2 summarizes the information pertaining to demographics and patient characteristics. The majority of cases (87.8%) was of Saudi nationality, and 76.6% were married. While the mean age for the entire cohort of patients was 45.95±10.12 years (range 21-65), cervical cancer patients were relatively older (49.88±8.62 years) as compared to the pre-cancerous lesion cases ( $p < 0.001$ ). Mean BMI of the reported cases was 29.81±7.03 kg/m<sup>2</sup>. Mean parity of the 329 reported cases was found to be 4.73±3.34 (range 0-18). Although over half of cases had educational level of High School and higher, but only 24.9% cases had employment status. Those with pre-cancerous lesions were more likely to smoke with an OR of 2.25 (1.002-5.06). Similarly, pre-cancer lesion patients had higher consumption of Oral Contraceptives OR=1.23(0.72-2.11). More than half of the cases 60.6% had the history of Pap smear, which they continued to do so. Cervical biopsy was performed on 74.1% of cases. Significant difference was seen when comparing previous and current Pap Smear and cervical biopsy with predominance in cervical cancer patients. All the cases were from the eastern region of oncology centers of the country (i.e., Al-Hasa , Dammam and Alkhobar areas). Also, 80.2% of patients were referred to oncology centers for treatment purposes.

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Factors	All Patients (N=363)	Patients with Pre- Cancer Lesion (N=264)	Patients with Cervical Cancer (N=99)	OR (95% CI)	P-value
Age, years(mean±SD)	45.95±10.12	44.48±10.26	49.88±8.62		<0.0001
BMI, kg/m <sup>2</sup> (mean±SD)	29.81±7.03	30.50±7.03	28.23±6.82		0.008
Data Access Group					<0.0001
IAU	53(14.6%)	49(92.5%)	4(7.5%)	Ref	
KFSH-D	129(35.5%)	40(31.0%)	89(69.0%)	27.26(9.21-80.69)	
NGH-A	181(49.9%)	175(96.7%)	6(3.3%)	0.42(0.11-1.55)	
Nationality					
Afghan	1(0.3%)	1(100%)	0(0%)		
Egyptian	2(0.6%)	2(100%)	0(0%)		
Indian	2(0.6%)	2(100%)	0(0%)		
Indonesian	3(0.8%)	2(66.7%)	1(33.3%)		
Irish	1(0.3%)	0(0%)	1(100%)		
Jordanian	3(0.8%)	3(100%)	0(0%)		
Malaysian	2(0.6%)	2(100%)	0(0%)		
Moroccan	2(0.6%)	1(50%)	1(50%)		
Philippine	16(4.4%)	15(93.8%)	1(6.3%)		
Saudi	317(87.3%)	228(71.9%)	89(28.1%)		
South African	4(1.1%)	3(75%)	1(25%)		
Syrian	2(0.6%)	2(100%)	0(0%)		
British	1(0.3%)	1(100%)	0(0%)		
American	2(0.6%)	1(50%)	1(50%)		
Bahraini	1(0.3%)	0(0%)	1(100%)		
Yamani	2(0.6%)	1(50%)	1(50%)		
Marital Status					0.003*
Single	3(0.9%)	0(0%)	3(100%)	4.8e <sup>9</sup>	
Married	278(76.6%)	208(74.8%)	70(25.2%)	Ref	
Divorced	24(7.3%)	16(66.7%)	8(33.3%)	1.49(0.61-3.62)	
Widowed	22(6.7%)	11(50.0%)	11(50.0%)	2.97(1.23-7.15)	
Age at marriage, years (mean±SD)	20.90±5.02	21.49±5.08	19.26±4.51		0.001
Parity (mean±SD)	4.73±3.34	4.51±3.29	5.33±3.42		0.048
Educational level					0.005
Illiterate	88(31.8%)	57(64.8%)	31(35.2%)	0.66(0.29-1.52)	
Elementary	31(11.2%)	17(54.8%)	14(45.2%)	Ref	
High school	83(30%)	68(81.9%)	15(18.1%)	0.27(0.11-0.66)	
College	67(24.2%)	51(76.1%)	16(23.9%)	0.38(0.15-0.94)	
Higher degree	8(2.9%)	8(100%)	0(0%)	0	
Job status					0.301
Employed	72(24.9%)	54(75.0%)	18(25.0%)	0.7(0.38-1.28)	
Unemployed	217(75.1%)	147(67.7%)	70(32.3%)	Ref	
Smoking	27(9.8%)	15(55.6%)	12(44.4%)	2.25(1.002-5.06)	0.068
Taking Oral Contraceptives	150(55.6%)	105(70.0%)	45(30.0%)	1.23(0.72-2.11)	0.497
History of Pap Smear	208(60.6%)	200(96.2%)	8(3.8%)	0.03(0.13-0.06)	<0.0001
Current Pap Smear	216(59.7%)	202(93.5%)	14(6.5%)	0.05(0.27-0.096)	<0.0001

Cervical Biopsy	269(74.1%)	175(65.1%)	94(34.9%)	9.56(3.75-24.36)	<0.0001
Region of Oncology Centers					<0.0001*
Al-Hasa	122(46.9%)	120(98.4%)	2(1.6%)	0.009(0.002-0.036)	
Dammam	132(50.8%)	45(34.1%)	87(65.9%)	Ref	
Riyadh	6(2.3%)	1(16.7%)	5(83.3%)	2.58(0.29-22.81)	

\*Fisher's Exact Test was used

**Table 2:** Demographics and patients' characteristics in pre-cancerous lesions and cervical cancer cases.

IAU = Imam Abdulrahman Bin Faisal University;

KFSH-D = King Fahad Specialist Hospital, Dammam;

NGH-A = National Guard Hospital, Ahsa;

SD = Standard Deviation;

BMI = Body Mass Index

A comparative summary of the data on clinico-pathological factors of patients with pre-cancerous lesions and cervical cancer is provided in Table 3. Nearly half of all the cases were of LSIL histopathology, followed by 27.3% of cases (n=103) with invasive cervical cancer (all the cervical patient group). Pre-cancer lesions were mostly LSIL (presented in 183 cases), followed by HSIL (64 cases) and AGUCS (17 cases). Tumor stage of the cervical cancer cases varied with mostly being of stage II, I, and IV respectively. HPV test was reported in only up to about 76 patients with a predominance in those with pre-cancerous lesions OR=2.21(1.3-3.78), and of those HPV-16 type was positive in 3 cases. Most cervical cancer cases 70.4% had SCC( Squamous cell carcinoma) histopathology followed by ADC (Adenocarcinoma) (21.4%).

Factors	All Patients (N=363)	Patients with Pre-Cancer Lesion (N=264)	Patients with Cervical Cancer (N=99)	OR (95% CI)	P-value
Type of Lesion					
AGUCS	17(4.7%)	17(100%)	0(0%)		<0.0001
HSIL	64(17.6%)	64(100%)	0(0%)		
Invasive Cancer	99(27.3%)	0(0%)	99(100%)		
LSIL	183(50.4%)	183(100%)	0(0%)		
Stage					
I	23(25.3%)	-	23(100%)		
II	31(34.1%)		31(100%)		
III	15(16.5%)		15(100%)		
IV	22(24.2%)		22(100%)		
Previous HPV Test	76(20.9%)	45(59.2%)	31(40.8%)	2.21(1.3-3.78)	0.004
HPV type					1*
16	3(15.8%)	3(100%)	0(0%)	0.52(0.08-3.09)	
Others	16(84.2%)	14(87.5%)	2(12.5%)	Ref	
Type of Cancer (Histopathology)					
Adenosquamous	1(1%)	-	1(100%)		
ADC	21(21.4%)		21(100%)		
Clear Cell	3(3.1%)		3(100%)		
SCC	69(70.4%)		69(100%)		
Serous	1(1%)		1(100%)		
Small Cell	3(3.1%)		3(100%)		

\*Fisher's Exact Test was used

**Table 3:** Summary of the clinico-pathological data for patients with pre-cancerous lesions and cervical cancer.

Data on the type of interventions received by the patients with pre-cancer lesion and cervical cancer are summarized in Table 4. The rate of intervention was the highest in colposcopy followed by surgery, chemoradiation, and chemotherapy, respectively. A total of 15% did not receive any interventions which were only pre-cervical lesion cases. Almost all cervical cancer cases received chemoradiation, surgical, chemotherapy, radiotherapy, and/or palliative care.

Interventions Received	All Patients (N=363)	Patients with Pre-Cancer Lesion (N=264)	Patients with Cervical Cancer (N=99)	OR (95% CI)	P-value
Colposcopy	107(29.5%)	107(100%)	-	0	
Surgery	96(26.4%)	63(65.6%)	33(34.3%)	1.59(0.963-2.64)	0.082
Chemoradiation	48(13.2%)	-	48(100%)		
Chemotherapy	10(2.8%)	-	10(100%)		
Palliative	8(2.2%)	-	8(100%)		
Radiotherapy	2(0.6%)	-	2(100%)		
No Intervention	52(14.3%)	52(100%)	0(0%)		<0.0001
Adjuvant treatment	20(6.1%)	-	20(100%)		
Type of Adjuvant Treatment		-			
Concomitant Chemoradiation	16(80%)		16(100%)		
Radiation Therapy	4(20%)		4(100%)		

\*Fisher's Exact Test was used

**Table 4:** Summary of the type of interventions received by the patients with pre-cancer lesion and cervical cancer.

Table 5 summarizes data on the type of surgery and lymphadenectomy performed for patients with cervical cancer. A total of 96 cases underwent such surgical procedures as LEEP, cone biopsy, simple hysterectomy, and/or radical hysterectomy. The overall death rate was 20.1% which was significantly higher in Patients with Cervical Cancer.

Procedures Performed	All Patients (N=363)	Patients with Pre-Cancer Lesion (N=264)	Patients with Cervical Cancer (N=99)	OR (95% CI)	P-value
Cone Biopsy	22(6.1%)	21(95.5%)	1(4.5%)	0.118(0.01 6-0.89)	0.014
LEEP	31(8.5%)	31(100%)	0(0%)	0	0.001
Radical Hysterectomy	20(5.5%)	0(0%)	20(100%)		<0.0001
Simple Hysterectomy	23(6.3%)	13(56.5%)	10(43.5%)	2.17(0.92-5.12)	0.071
Follow-up	143(44.7%)	83(58.0%)	60(42.0%)	3.41(2.04- 5.67)	<0.0001
Death	36(20.1%)	5(13.9%)	31(86.1%)		<0.0001

\*Fisher's Exact Test was used

**Table 5:** Summary of the surgery type and lymphadenectomy performed for patients with cervical cancer.

LEEP = Loop Electrosurgical Excision Procedure

## Discussion

Cervical cancer is a potentially preventable disease, and its progression can be stopped through detection of the pre-malignant lesions at an early stage. This aspect makes this study essential, especially in a developing country like ours where there is dire lack of adequate screening programs. Many previous studies emphasize the importance of detecting pre-cancerous cervical lesions by pap smear at an early stage. As a result various health screening programs have also been launched. In Saudi Arabia, cancer cervix screening program is not launched yet as a well-organized national program as the case of breast cancer. (21) As per the recommendations of the American Cancer Society (2012), Pap smear with an HPV DNA test is a screening method that should be performed every five years, while Pap smear, as a routine method for detecting cancer, is recommended to be performed every 3 years.. (27) HPV testing in our study was reported in only around one fifth of the patients, which might indicate a low awareness in the study population of HPV associated risk of cervical cancer. Some previous studies have reported a similar lack of awareness as well. (22,23).

The relative frequency of HPV-16 type infection increases with the severity of lesions from atypical squamous cells of undetermined significance (ASCUS; 6–27%) to low-grade squamous intra-epithelial lesions (LSIL; 16–32%) to high-grade squamous intra-epithelial lesions (HSIL; 41–67%), and accounts for 71% of invasive cervical cancers worldwide [Alsbeih et al 2011]. However, the prevalence of HPV in Saudi Arabia is 10.4% [Alsbeih et al 2011] with a relatively higher frequency of HPV-16, -18, -45, and -31, respectively [ICO/IACR Fact Sheet 2018]. This shows that the association between the HPV genotype and pre-cancerous lesions and cervical cancer is not well documented in Saudi Arabia, including in the Eastern Province of the Kingdom. Also, the country/region lacks HPV vaccination as part of the routine immunization program.

Past studies have reported several risk factors that cause cervical cancer in women like viral infections, multiparity, early sexual activity, smoking, multiple sexual partners, low socioeconomic status and long-term use of oral contraceptives along with immunosuppressive medicines. (24) This study too showed a similar pattern as smoking and oral contraceptive use posed a great risk to development of advanced disease. Despite several risk factors (such as multiple marriage events, multiparity, early age of first intercourse, etc.), it is historically well known that the prevalence of cervical cancer is relatively low among Muslim women due to various obvious reasons as noted by El Dosoky et al [1995]. The reasons for this could be due to the fact that fewer Muslim women were willing to come to the hospital because of their religion and conservative culture.

In Saudi Arabia, cervical cancer ranks as the 8th leading cause of female cancer (particularly affecting the women of age 15–44 years) [ICO/IACR 2016]. According to a recent ICO/IACR Fact Sheet [2018], it is estimated that every-year > 300 cases with cervical cancers are diagnosed and roughly half of them would die due to the disease. Despite the fact that Saudi Arabia, as a nation, has excellent healthcare

facilities; information regarding the understanding of the disease screening/prevalence in the Eastern Province of the Kingdom is not adequate. Findings showed that there were only low-to-moderate level of awareness about the disease diagnosis, prevention, and/treatment options available to the population. Previous peer-reviewed studies from Saudi Arabia's other regions have also observed somewhat similar experience, such as the survey among medical students of the KFU-A [Al-Darwish et al 2014], women in Riyadh City [Al Khudairi et al 2017], and in the Qassim region [Alnafisah et al 2019]. Hence, organized screening programs are desirable to establish / validate the prevalence of women with pre- cancerous lesions and cervical cancer in the region (as has been proven successfully in the developed/western countries for decades). A health educational intervention program is also needed that can be nestled within the screening program to address the understanding of the factors that lead to cervical cancer, especially amongst the lower socioeconomic class and unemployed.

Pre-cancerous cervical lesions and cervical cancer have many co-factors, among which are human papillomavirus (HPV), lack of screening programs, lack of awareness of the disease and its consequences, herpes simplex virus co-infection, and human immunodeficiency virus (HIV) infection [Al Harfi et al 2019; Jradi et al 2019]. The use of HPV screening has the advantage of transition of cervical cancer screening from pure subjective evaluation of morphology to the more objective molecular biology. The HPV test was initially used as a classification method for the reflex analysis of atypical squamous cell populations of undetermined significance (ASCUS). Since 2014, the FDA has approved HPV screening to be used as a first line screening for cervical cancer (20)

Unlike developing countries, experiences in developed countries have shown that healthy lifestyles, such as health information and warnings about tobacco, sex education adapted to age and culture, promotion / provision of condoms for sexual activities, HPV vaccination, well-planned and organized screening programs with high coverage can significantly reduce the new cases of cervical cancer and the associated mortality rate. This study has been conducted to emulate and tackle this issue. (25)To our knowledge, this is the largest study evaluating collected dataset for a long period (>10-years) from various multiple centers about the prevalence of pre-cancerous lesions and cervical cancer cases from the eastern region of Kingdom. Roberts et al (26) found a positive relationship between the education level and awareness and execution of timely screening. In present findings, cervical cancer patients were less educated compared to pre-cancerous patients who had more illiterate population. This can be possibly associated to the more conservative attitude of this cohort . Yet, the maximum patient population in this study was illiterate which goes well with the general demographic of a developing country and does not influence the results of this study. However, the study does have some limitations. First, it has a relatively small sample size and cross-sectional design, which is less potent than a cohort study. Increasing the sample size would make this study more generalized. Since only hospitals in the Eastern Province of the Kingdom were included, the results don't necessarily reflect the status of the entire population of Saudi

Arabia. The study was limited to these hospitals because they are considered as the reference hospitals in the studied region.

### **Conclusion**

As a take away message, this study can act as an anchoring point to guide national screening programs in the future. But until they are established, other measures can be implemented like awareness campaigns led by media to increase motivation and awareness of risk factors for women, and a temporary opportunistic screening program. The responsibility for this would lie on the health care workers who would need to refer all eligible women in their care for cervical cancer screening and ensure a proper follow up.

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