

Cervical Cancer Prevalence at King Abdulaziz University Hospital

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Abstract: Introduction: Cervical cancer (CC) is the tenth most frequent cancer in females in Saudi Arabia. Squamous intra epithelial changes are increasing in the recent years in many reports from different regions of the Kingdom. However, no information on the frequent histopathological types of CC. **Objective:** The objective of this study is to identify the most frequent histopathological types of CC diagnosed at King Abdulaziz University Hospital (KAUH) and to compare it with literature. **Methods:** A retrospective study was designed to reclassify all cases that were diagnosed as CC by using the World Health Organization (WHO) classification system at the Department of Pathology of KAUH from January 1990- September 2012. We identified and reclassified 167 cases. **Results:** The most frequent type was Squamous cell carcinoma (83%) followed by adenocarcinoma (7.7%) and then adenosquamous (3.6%). The Non keratinizing and keratinizing squamous cells are of nearly equal distribution in frequency and age (32% versus (30%) with mean age of 50 years versus 54 years. Adenocarcinoma tends to be presented at slightly earlier age. **Conclusion:** Cervical carcinoma occurs in matching frequency with major histological type and age group in literature although the keratinizing and non keratinizing are almost similar in prevalence which is different than other reports. Lack of CC screening program and research in this area obscure a lot of information of the natural history of this health problem in this part of the world.

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1. Introduction:

Our understanding of CC has changed a lot after series of publications in this aspect. It is well documented in the literature that CC has many risk factors; top of the list is Human Papilloma Virus infection (HPV) (1). The viral infection will cause series of cytological changes in cervical epithelium that can be detected by cytological examination of the cervix by Pap smear. Its incidence was the second cancer of the females in Western Societies in the early sixties, and nowadays it drops down to eight (2-6). In the United State of America, according to the National Cancer Institute (NCI), it is estimated that 11,270 women were diagnosed with cancer of the cervix uteri in 2009; about 4,070 women died of it (7). Its incidence is higher in Hispanics and black in comparison to Asian/Pacific Islander and Whites. The mortality rate was higher in Black American in comparison to the other ethnic groups. The median age of diagnosis of cervical cancer was 48 years.

In Canada, Incidence rates of cervical cancer have declined dramatically over the last 3 decades, from 19.4 per 100 000 women in 1971 to 8.4 per 100 000 women as estimated in 2000 (8). Dr Liu *et al.*, reported that the overall age-adjusted incidence rates of cervical squamous cell carcinoma declined by 51%, from 13.39 per 100 000 women in 1970–1972

to 6.56 per 100 000 women in 1994–1996. Conversely, incidence rates of adenocarcinoma and adenosquamous carcinoma increased considerably, from 1.30 and 0.15 per 100 000 women respectively, in 1970–1972, to 1.83 and 0.41 per 100 000 women respectively, in 1994–1996. Further analysis showed that the observed increase in overall incidence rates of adenocarcinoma and adenosquamous carcinoma was mainly in women aged 20–49 years (9).

In Saudi Arabia (SA), the World Health Organization (WHO) currently estimates that women population of 6.5 million are at age 15 years and older, and they are at risk of developing cervical cancer, which ranks as the 11th most frequent cancer among females in SA in general.

It is the 8th most frequent cancer among women between 15 and 44 years of age (10). According to Saudi cancer registry of 2001(NCR) report, carcinoma of cervix rank number tenth preceded by cancer of breast, thyroid, leukemia, lymphoma, brain, colon, oral cavity, ovary and Hodgkin lymphoma. Its prevalence is 3% and Age Specific Rate (ASR) is 2/100,000 female population (11). No recent data from NCR of cervical cancer prevalence in their 2006 report.

WHO recognize more than 30 histological types of CC (12). In this study we tried to reevaluate all the

cases of carcinoma of cervix by reclassifying them based on WHO histopathology classification (12&13)

2. Material and Methods:

We used the data base of Phoenix System which is available in Anatomical pathology laboratory, to identify the cases with cervical biopsies that had cervical cancer diagnosis or carcinoma *in situ* in the archives of the Department of Pathology King Abdulaziz University Hospital. We also used the manual search of the old cases (from 1995-1990). The list of the cases and the slides were prepared for the pathologist (authors) to examine them. We excluded cervical biopsies with the diagnosis of cervical intraepithelial neoplasia(CIN I& CIN II), endometrioid carcinoma of endometrial type that presented as cervical mass, or even adenocarcinoma

of cervix (endometrioid) type that cannot be differentiated histopathologically from endometrial type based on the material submitted.

The hematoxylin and eosin stained (H&E) slides of each case were reviewed and reclassified according to modified World Health Organization (WHO) of invasive carcinoma of the uterine cervix by two of the authors (FA &GM).

3. Results:

A total of 167 cases were found with the diagnosis of carcinoma of cervix. Some cases had single histopathology diagnosis (n=147), others had multiple specimen over a period of time (n=20), but the diagnosis was based on one specimen and they are counted as one case. The different histological types that we identified were tabulated in table II.

Table I: Modified World Health Organization (WHO) histological classification of invasive carcinomas of the uterine cervix

1- Squamous cell carcinoma – Keratinizing / Non-keratinizing	
	Microinvasive squamous cell carcinoma
	Invasive squamous cell carcinoma
	Verrucous carcinoma
	Warty (condylomatous) carcinoma
	Papillary squamous cell (transitional) carcinoma
	Lymphoepithelioma-like carcinoma
2- Adenocarcinoma	
	Mucinous adenocarcinoma
	Endocervical type
	Intestinal type
	Signet-ring type
	Endometrioid adenocarcinoma
	Endometrioid adenocarcinoma with squamous metaplasia
	Clear cell adenocarcinoma
	Minimal deviation adenocarcinoma
	Endocervical type (adenoma malignum)
	Endometrioid type
	Well-differentiated villoglandular adenocarcinoma
	Serous adenocarcinoma
	Mesonephric carcinoma
3- Other epithelial tumors	
	Adenosquamous carcinoma
	Glassy cell carcinoma
	Clear cell adenosquamous carcinoma
	Mucoepidermoid carcinoma
	Adenoid cystic carcinoma
	Adenoid basal carcinoma
	Typical carcinoid tumor
	Atypical carcinoid tumor
	Large cell neuroendocrine carcinoma
	Small cell carcinoma
	Undifferentiated carcinoma

Table II: KAU cases Histopathological type identified, mean age & Frequency

Histological Types	N	%	Mean Age	Std. Deviation
Squamous cell carcinoma, non-keratinizing	54	32.1	50.7037	14.54937
Squamous cell carcinoma, keratinizing	51	30.1	54.2353	13.51531
Microinvasive squamous cell carcinoma	1	0.6	30.0000	
Invasive squamous cell carcinoma	1	0.6	29.0000	
Carcinoma in-situ / CIN III	32	19.6	44.2500	11.98655
Invasive papillary squamous cell carcinoma	1	0.6	40.0000	.
In-situ adenocarcinoma	1	0.6	58.0000	.
Invasive adenocarcinoma endocervical type	12	7.1	48.0000	10.35725
Adenosquamous carcinoma	6	3.6	47.8333	11.90658
Papillary serous adenocarcinoma	2	1.2	56.5000	6.36396
Mucoepidermoid carcinoma	2	1.2	51.5000	16.26346
Invasive adenosarcoma	2	1.2	70.0000	.00000
Small cell carcinoma	1	0.6	38.0000	
Undifferentiated carcinoma	1	0.6	46.000	.
Total	167	99.4	50.2048	13.73053

4. Discussion:

The most common histological types of Cervical Carcinoma in the literature is the squamous cell carcinoma (SCC) accounted for 75-80% of CC with a mean age 55 years. The next common type is adenocarcinoma 20-25%, followed by adenosquamous and small cell carcinoma (12, 13). Majority of SCC are non-keratinizing, which means it lacks squamous pearls but individual cell keratinization is evident in most of the cases. The keratinized SCC contains squamous pearls and may also show individual cell keratinization. The risk factors of CC are as for squamous intraepithelial changes (SILs). WHO recognizes three major types of Cervical Carcinoma (CC) and 31 histological subtypes, as demonstrated in table I (12).

There are many reports from different provinces of the Kingdom mainly from Western region, and they are all hospital based studies (10&16-19). These reports indicate there is a definite increase in the prevalence of cervical epithelial changes in PS from (1.6% to 7.9% and recently 17.3%). Which reflect an increase in the incidence of HPV infection.

Study from the Eastern province also indicates an increase of squamous epithelial changes (SIL) up to 4.9% seen in PS (20).

Few studies had looked at the presence of HPV in cytology by molecular methods (21) and found 5% of the cervical smears have oncogenic HPV.

Al-Muammar *et al.*, looked also at HPV DNA in cytology specimen and correlates it with PS. Of the 120 samples used in their study, 38 (31.6%) were found positive by PCR for HPV-16 or HPV-18 or both (22). When they correlated that finding with the cytology they found 10 cases (8.3%) showed minor cytological changes (reactive and reparative changes, inflammatory cellular changes, and low-grade squa-

mous epithelial lesions [LGSL]) in the Pap smear test. Of these 10, only 6 were HPV-infected (1 HPV-16, 1 HPV-18, and 4 HPV-16/18), making the prevalence of HPV 60% (6/10) in those with cytological changes and 5% (6/120) in all subjects. Very much similar result to Gazaz study in the Western region 6% HPV DNA detected in cervical cytology (21).

Al Hebishy *et al.*, looked at the prevalence of HPV virus DNA in 100 cases that have the diagnosis of cervical cancer. They concluded that eighty-nine percent of cervical cancers in Saudi Arabia were associated with HPV infection, and 78.7% (70/89) of HPV-positive tumors were infected with HPV-16/18, which caused the cancer to appear 5 years earlier than the combined HPV-negative and other HPV genotypes ($P=0.013$). (23)

We did not find a single study in Saudi Arabia that looked at the frequency of the histological types of cervical cancer and to compare it to literature.

We found no much difference in the prevalence between the non Keratinizing and keratinizing squamous cell carcinoma 32&31%. In addition no big differences in their mean age as well 51 versus 54 years. The literature review reveal there is difference in the prognosis in the treatment of the 2 groups when radiotherapy is a modality of treatment. Keratinizing SCC is less sensitive to radiotherapy in comparison to non keratinizing SCC and subsequently to survival (24).

The in situ cancer of squamous component in our study represent 20% (32/167) with mean age of 44 years, which is younger than the invasive SCC and still older than literature, the reason of this could be due lack of detection earlier as a result of absence of cervical cancer screening program or it could be

related to the disease natural history in this part of the world.

Invasive adenocarcinoma represented 7% of our cases. It is presenting few years earlier than invasive SCC (48 years) but no big age difference as reported in literature

Liu *et al.*, (9) reported in their study that several reports from Sweden, United States, and Australia have reported an increase of incidence of invasive cervical adenocarcinoma, although the overall incidence of cervical cancer has declined. It accounts for 10%–15% of all cervical cancers and it has been increasing in young women (age range 29-49yrs.). The cause of the increase is unclear, but the possibly of Changes in sexual habits and increased transmission of HPV, but it are of concern because some studies have shown a poorer prognosis for patients with cervical adenocarcinoma than for those with squamous cell carcinoma. At the time of diagnosis, adenocarcinoma tends to be larger and exhibits a propensity for early lymphatic and hematogenous metastasis (25).

We identified 2 cases of serous carcinoma (1.2%) with average age of 56 years and both of them present with stage IV disease. It is a rare type of endocervical adenocarcinoma. Serous carcinoma of the cervix occurs much less frequently than serous carcinoma of the endometrium. Only one series with a significant number of patients has been reported and it contained only 17 cases (26). In one study, serous carcinoma did not appear to be associated with HPV infection. (27)

Serous carcinoma of the cervix occurs over a wide age range, but there appears to be a bimodal distribution, with a peak <40 years and another >65 years. (26) The typical clinical presentation is with abnormal vaginal bleeding or an abnormal Pap smear. Treatment has been the same as for other types of cervical carcinoma. In the largest series 6 of 15 patients died of carcinoma, an outcome similar to that observed in adenocarcinoma of the cervix overall. Serous carcinoma can occur as a pure type or a second type of cervical adenocarcinoma can be admixed.

Since serous carcinoma of the endometrium is much more common than serous carcinoma of the cervix, endocervical spread of an endometrial serous carcinoma must be excluded before a diagnosis of serous carcinoma of the cervix is made (26).

Papillary squamous cell carcinoma is a type of squamous cell carcinoma that grow in thin and thick papillae with fibrovascular core and the epithelium mimicking that of high grade squamous intraepithelial lesion. (28). typically this tumor occurs in women in the late reproductive period or postmenopausal age group. Mirhashemi et al reported

presence of HPV antibodies in 50% of their cases. (29)

Declaration:

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