EPITHELIAL OVARIAN CANCER;
EPIDEMIOLOGY AND CLINICOPATHOLOGICAL FEATURES

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ABSTRACT...Background: Epithelial ovarian cancer is the most common cancer of gynaecologic origin in Pakistani women. It ranks among the ten most common cancers in our women. Despite being commonly encountered, information regarding the clinicopathological features is lacking. Objective: To study the clinical and pathological features of epithelial ovarian cancer in our patients. Study Design: Retrospective study. **Setting:** Department of Medical Oncology, Jinnah Hospital Lahore. **Period:** Jan 01,2001 to Dec 31, 2002. **Patients and methods:** All patients with histological or cytological diagnosis of epithelial ovarian cancer regardless of stage were included in the study. Information was obtained from medical records which were reviewed thoroughly. Blood samples for analysis of BRCA mutations were sent to University of Toronto, Sunnybrook & Women's College Health Sciences Centre, Toronto, Canada. **Results:** 75 patients were accrued. Mean age of the patients was 47 years. The well defined risk factors such as nulliparity, lack of lactation, early menarche and late menopause were not present in the majority of our patients. One striking feature was the number of patients with family history of cancer (18.7%). Majority were first degree relatives of the patients and most had ovarian or breast cancer. BRCA1 and BRCA2 were seen in nine (12%) of the patients. Clinical presentation and histologic features were similar to American and European patients, the only difference was that a large number (88%) of our patients presented with advanced (stage III or IV) disease. **Conclusions:** Epithelial ovarian cancer manifests itself in a younger population of our women. Higher frequency of positive family history was another striking feature of Pakistani patients.

Key words: Ovarian cancer, clinicopathological features, family history.

INTRODUCTION

Epithelial cancers of the ovaries account for about 90% of ovarian malignancies. It is the leading cause of death from a gynecologic cancer[1]. The incidence of ovarian cancer appears to vary by race, being more common in Caucasians than African-Americans. There are also geographic variations in the incidence of ovarian cancer, with the highest rates found in industrialized countries.

Ovarian cancer is particularly frustrating as the incidence as well as the number of deaths from this cancer has been gradually rising for several decades . Incidence has been rising about 1-2% per year in several countries[2]. In Pakistan, ovarian cancer is the most common gynecologic cancer[3,4] and ranks from second to fifth in various Pakistani studies among the ten most common cancers in our women[5,6,7,8].

Ovarian cancer is seen mainly in the post menopausal women, commonly in the sixth and seventh decade of life. The predisposing factors are mainly genetic, though hormonal and environmental factors may also play a role in the development of this deadly disease. Reproductive history like early menarche, late menopause and nulliparity are particularly considered to be important as are age, ethnicity, lack of lactation, personal history of breast or endometrial cancer and family history of breast or ovarian cancer[9]. The most significant risk factor, however, is a family history of disease. Recent advances in molecular genetics have found mutations in the BRCA1, BRCA2, MLH1, MSH2, PMS1 and PMS2 genes, accounting for 10-15% of ovarian cancer cases[9].

Relatively little is known about the epidemiology of ovarian cancer despite the high prevalence of the disease. It is one of the major problems confronting gynecologists and oncologists as it is the most common and fatal gynecologic malignancy. This study presents information collected on 75 patients with epithelial ovarian cancer with the purpose of highlighting the clinicopathological features of this disease.

PATIENTS AND METHODS

The study was conducted at the Department of Medical Oncology, Jinnah Hospital Lahore, affiliated with Allama Iqbal Medical College. Information was retrospectively collected on all patients with epithelial ovarian cancer referred to our department between Jan 01, 2001 and

Dec 31, 2002. The medical records were thoroughly studied. Blood samples of the patients were sent to the laboratory of University of Toronto, Sunnybrook & Women's College Health Sciences Centre, Toronto, for BRCA analysis. Human genomic DNA was isolated from 20ml of peripheral blood. A variety of methods were employed to detect the presence of a BRCA1 or BRCA2 mutation. Exon 11 of BRCA1 and exons 10 and 11 of BRCA2 were screened by protein-truncation testing (PTT) , in all case subjects. All mutant bands detected by PTT were confirmed by direct sequencing.

RESULTS

75 patients were accrued to the study. The mean age of the patients was 47 years. About two-thirds (62.6%) of the patients were younger than 50 years at the time of diagnosis. 89.3% of the patients were premenopausal and only 20.7% were postmenopausal.

Most belonged to lower and middle socioeconomic class and were illiterate. Regarding personal habits, only 4% of the patients smoked or chewed tobacco, and none had been exposed to any kind of radiation. A small number of patients (15) used hormones for contraception or other purpose.

Mean age at menarche was relatively late (13.2 years). Majority of the patients were married (93.3%) and 80% did lactate for more than six months of duration per pregnancy. Mean number of pregnancies was 4.1. Eleven (14.6%) patients were nulliparous. 24% (18) of all patients in this study had consanguineous marriages.

Only 4 (5.3%) patients had previous history of cancer. Out of these, three had breast cancer and one patient had history of carcinoma of the colon.

Fourteen (18.7%) patients had family history of cancer. Nine (64%) of these were first- degree relatives of the patients and seven had either breast or ovarian cancer.

BRCA1 and BRCA2 mutations were seen in nine (12%) of the patients. Eight of these had BRCA1 mutations and one patient had BRCA2 mutation. BRCA1 mutations were at these sites; exon 11 1956delA, exon 11 2041insA, exon 2 185insA, exon 15 S1503X, exon 11 3889delAG, exon 11 1127delA, exon 11 2266delG and exon 11 S868X. BRCA2 mutation was found at exon 11 6679insAA.

Pre treatment CA 125 was raised in 49 (65.3%) patients. Most (53.2%) of the tumors were grade II and III, and serous cystadenocarcinoma was the predominant histology. Majority (88%) of the patients had stage III or IV disease at the time of presentation.

DISCUSSION

Ovarian cancer is one of the most important gynecologic cancers and also the most common cause of death among all gynecologic malignancies[1]. It causes death of more American women each year than all the other gynecologic cancers combined[10]. These constitute 23% of all gynecologic tumors[1]. Several local studies have shown that gynecologic malignancies are not uncommon among Pakistani women, ovarian cancer being the most common[11,12]. However little information is available regarding the epidemiology and clinicopathological features of epithelial ovarian cancer in our patients.

The aim of this study is to determine the clinicopathological aspects of ovarian cancer in our patients and to correlate our findings with national and international published data.

Mean age of 47 years was seen in our patients at the time of diagnosis. In Western literature mean age of 61 years has been reported in patients with epithelial ovarian cancer[13]. However younger age of 48 years has been reported in patients with BRCA1 mutations[14]. In our patients, younger age at the time of diagnosis has been reported in several studies. In one of the studies, the mean age of the patients with epithelial ovarian cancer was 49.5 years[15]. In another study, the mean age of women with malignant epithelial neoplasms of the ovary was 43 years[11]. This is similar to Japanese, Chinese and Indian women and significantly lower than Caucasian women in Europe or North America. Also this age is lower than Turkish or Norwegian studies in which a median ages were 57 years and 59 years respectively [16,17]. Life expectancy of our people is lower than that observed in

the West. This could be one of the reasons of disease manifesting in a younger age group.

Most of the patients included in this study belong to lower socioeconomic class. This could be because this study was conducted in a governmental institution where majority of the patients are needy and poor. Most lacked education and belonged to rural area.

The established risk factors for ovarian cancer were not frequently seen in these patients. Very few patients had early menarche, late menopause, nulliparity or advanced age at first childbirth. Parity was high and most patients had established lactation. Use of oral contraceptives was rarely seen.

In this study, 18.7%[14] of the patients had positive family history for cancer. Majority of them (>50%) were first-degree relatives, with breast and ovarian cancer. It seems that genetic factors may be responsible in the development of ovarian cancer in our patients. This probably accounts for the younger age at diagnosis in these patients. High incidence of positive family history in patients with ovarian cancer has been seen in several local studies. In one of the studies, 20% of the patients with epithelial ovarian cancer had positive family history for cancer[15]. Several studies have shown that positive family history of cancer does not confer a high risk for the development of ovarian cancer in Chinese and Indian women[18,19]. Consanguinity plays a role in the transmission of genetic disorders. Consanguineous marriages are common in our country. 24% of all patients in this study had consanguineous marriages.

Only four (5.3%) patients had previous history of cancer. Out of these, three patients had breast cancer and one patient had history of carcinoma of the colon.

BRCA1 and BRCA2 mutations were seen in nine (12%) patients. Eight patients had BRCA1 mutations and BRCA2 mutation was seen in only one patient. One of the BRCA 1 mutation, 185insA, has been identified previously in Pakistani breast and ovarian cancer patients. The mutation analysis covered about 70-80% of mutations in either BRCA1 or BRCA2.

Among the BRCA positive patients, seven patients were 50years of age or younger and only two patients were >50 years old. This correlates with published data. Several Western studies have reported younger age in BRCA positive patients diagnosed with epithelial ovarian cancer. Two (22.2%) patients had positive family history. Both were first-degree relatives of the patients; one had breast cancer and the other had ovarian cancer. Out of the three patients who had previous history of breast cancer, two were found to have BRCA mutations. One had BRCA1 and the other had BRCA2 mutation.

Clinicopathological features are consistent with those reported in the literature. Symptoms at presentation and laboratory features of our patients are quite characteristic of the disease. Abdominal pain and distention were the main presenting complaints. 74.6% (56) of the patients had symptoms of abdominal pain and almost equal number of patients (57) complained of abdominal distention. Abnormal vaginal bleeding was seen in only seven patients and vague symptoms of lower abdominal discomfort, urinary complaints and nausea and dyspepsia were seen in thirty two (42.6%) patients.

No marked variation in the histologic features was observed. Serous cystadenocarcinoma was the predominant histology in our patients (53.3%) (Table I). Tumors of the serous type constitute 46% of all epithelial cancers[20]. Several local studies have shown serous cystadenocarcinoma to be the commonest of the malignant surface epithelial tumors followed by the mucinous and endometrioid carcinoma[11,15]. In one of the local studies, 33.33% of the tumors were serous cystadenocarcinomas[11]. However, in some local studies, mucinous cystadenocarcinoma was the commonest malignant epithelial tumor followed by the serous type of tumors[21]. It seems that mucinous tumors are more common in our population as compared to the west where endometrioid carcinoma ranks second behind serous adenocarcinoma[22,23]. The reason for this is not clear; it could simply be a geographical variation.

The percentage of serous tumors is slightly higher in our patients and that of mucinous tumors lower when results are compared to an Egyptian study in which 46.8% were

Table-I. Clinicopathological features of women with ovarian cancer (n=75)

Variable		No.	%age
(Median 47 years)	<50 years	47	62.6
	>50 years	28	37.4
Positive family history		14	18.7
Menopausal status	Premenopausal	67	89.3
	Postmenopausal	08	20.7
Stage at presentation	I	03	4.0
	II	06	8.0
	III	45	60.0
	IV	21	28.0
Pathological grade	Well differentiated	15	20.2
	Moderately differentiated	23	30.6
	Poorly differentiated	17	22.6
	Unknown	20	26.6
CA 125	Abnormal	49	65.3
	Normal	07	9.3
	Unknown	19	25.3

Table-II. Clinical features

Variables	No.	%age
Abdominal pain	56	74.6
Abdominal distention	57	76.0
Abnormal bleeding per vaginum	07	9.3
Other symptoms	32	42.6

Table-III. Family history

Variables	No.	%age
Positive family history	14	18.7
BRCA mutations	09	12.0

serous adenocarcinomas and 32.2% were mucinous[24]. Similarly, an Italian study shows serous carcinomas to be the commonest constituting 44.6% of all histologic types and 29.7% were mucinous[25].

Approximately 23% of the patients in this study had poorly differentiated tumors. This is lower than the Florence (30.6%) and a Californian study (49%)[26,25]. Another study reports that 39% of their patients had poorly differentiated tumors[24].

Eighty-eight percent of our patients presented with stage III or IV disease. Though most of the patients with epithelial ovarian cancer are diagnosed in advanced stages of the disease because of vague symptoms and signs initially, this percentage is quite high. In one of the local studies, 78% of the patients had stage III or IV disease at the time of diagnosis. Several factors contribute towards late presentation including lack of health education and disease awareness in our patients and financial constraints due to which patients do not seek medical attention in the early course of disease. Our findings are consistent with studies conducted in Berlin[27] and Israel[28], which have also shown that the majority (50-70%) of the cases were diagnosed in stage III or IV.

CONCLUSIONS

In conclusion, the clinicopathological features and biologic behaviour of epithelial ovarian cancer in Pakistani women are similar to what has been reported in the Western literature. However, a higher percentage of women present in advanced stages of the disease in our country. Health education programmes are needed for the awareness of the masses about the disease, and access to medical facilities should be easy and cheap. These measures will help in diagnosing the disease in early stages when a high percentage of cases are curable.

Most of the established risk factors like nulliparity, early menarche, late menopause and lack of lactation were not commonly observed in our patients.

Majority of our patients present at a younger age and a higher frequency of positive family history is seen. This indicates a more significant role played by genetic factors

in these patients. Further research is needed in this respect.

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