RESEARCH COMMUNICATION

Incidence, Trends and Morphology of Ovarian Cancer in Karachi (1995-2002)

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Abstract

  <u>Introduction</u>: Cancer ovary is the third most common malignancy diagnosed in women in Karachi, a moderate to high risk region for the disease. <u>Materials and Methods</u>: Three hundred and thirty seven cases of ovarian cancer registered at the Karachi Cancer Registry for the years 1995-2002 were reviewed. <u>Results</u>: The age-standardized incidence rate (ASR) world per 100,000, crude incidence rate per 100,000 (CIR) and frequency of ovarian malignancies in 1995-1997 were 10.9, 5.9 and 6.2% respectively. Corresponding figures for 1998-2002 were 8.1, 5.1 and 4.8%. The mean age at presentation in 1995-1997 was 45.7 years (95%CI 42.9, 48.4; SD±15.9), range 95 (3 to 98) years and in 1998-2002 it was 45.0 years (95%CI 42.8, 47.3; SD±16.1), range 79 (3 to 82) years. Eleven (3.3%) cases of childhood cancers, 13 (3.9%) adolescent cases, 126 (37.4%) reproductive age (20-44 years) and 187 (55.5%) cases in the 45+ age group were registered. Epithelial malignancies were the most common cancers above the age of 20 years (78.4%), the commonest amongst these was serous adenocarcinoma (33.3%). Germ cell tumors were more common (5.6%) in children and adolescents. Microscopic confirmation was 99.0%. Presentation was of a moderately differentiated (grade 2) malignancy with a regional or distant spread of disease in three fourths of the cases. <u>Conclusions</u>: The incidence of cancer ovary, though stable in Karachi, involves a relatively younger age group with a strong family history in a fourth of the cases. The disease presents at an advanced stage. An ageing population over time may translate into a higher incidence of ovarian cancer. The current incidence of cancer ovary in Karachi is an enigma and belies reproductive protective factors. Studies focused on the genetic risk factors in this population are recommended.

Keywords: Cancer of the ovary - Karachi, Pakistan - incidence - trends

Introduction

Primary cancer of ovary is the sixth most common malignancy diagnosed globally in women and accounts for approximately 4.0 percent of cancers (Parkin et al., 2005). It has the worst prognosis of any gynecological cancer, because it produces no symptoms until it is at an advanced stage.

Higher incidence rates of ovarian cancer (exceeding 9 per 100,000) are reported for developed countries. The highest age standardized incidence rates per 100,000 (ASR/100,000) for the years 1993-1997 were reported for Switzerland (16.9), Iceland (16.7), Israel, Jews (16.5), Sweden (15.7) and England (15.3) (Parkin et al., 2002). In the years 1998-2002 the highest rates were reported for Argentina (16.0), Poland, Northern Ireland, Lithuania (15.0) and the Czech Republic (14.0) (Curado et al., 2007).

A lower incidence is reported for Africa and Asia (Parkin et al., 2005). During 1993-1997, the lowest incidence (ASR per 100,000) was reported for China (2.3), Mali (2.1), Korea (2.0) and Gambia (2.0) (Parkin DM et al, 2002). The lowest incidence rates in 1998-2002 were reported for China (4.0), Israel, Non-Jews (3.8), Tunisia (3.5) and Algeria (2.1) (Curado et al., 2007).

The current study was conducted to determine the incidence and trends of ovarian cancer in Karachi, for the periods 1995-1997 and 1998-2002. No population-based data on ovarian cancer has been published for Pakistan.

Materials and Methods

Data of ovarian malignancies ICD-10 categories C56 registered at Karachi Cancer Registry (KCR) for

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Karachi South (KS), during 1st January 1995 to 31st December 2002 were reviewed and analyzed as two time periods 1st January 1995 to 31st December 1997 (period 1) and 1st January 1998 to 31st December 2002 (period 2). Beginning with data from 1995, KCR includes all incident cancer cases diagnosed in permanent residents of Karachi South, the southern-most district of Pakistan. Data were collected in accordance with the guidelines of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR) (Parkin et al., 1994) since the registry's inception (Bhurgri et al., 2000).

The current study included clinically diagnosed and microscopically verified cases. Histologically verified cases were initially evaluated on hematoxylin and eosin (H&E) stained sections. Special stains and immunohistochemistry were selectively used. Manual and computerized validity checks for the cancer data were performed as per recommendations of IARC and IACR (Parkin et al., 1994). These included checks for multiple primaries and duplication. Cases were categorized by tumor site, and age of the patients. Variables recorded were the hospital patient-number, date of incidence, name, age, address, ethnicity, topography, morphology, grade, stage and date of death/last follow-up.

Sources of incidence data were hospitals, laboratories and death registries within Karachi South, as well as other districts of Karachi. Case ascertainment is thought to be nearly complete for the entire study period. Data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-4 software. Crude, age standardized incidence rate (ASR) and age specific incidence rates were calculated using person years of population at risk by sex and 5-year age-groups, based on the 1998 census; population of 893,684 males and 794,920 females, assuming an annual growth rate of

1.94%, as calculated by the Federal Bureau of Statistics. Majority of the cases were confirmed by histopathology of the primary cancer. A few cancers diagnosed clinically at an advanced stage were confirmed by histopathology or cytology of metastasis.

The definition of incidence used was 'number of new cases, expressed as an absolute number of cases per year or as a rate per 100,000 persons per year'. The latter approximates the average risk of developing a cancer in one year and is used for comparisons between countries or world areas, or within populations over time (Parkin DM et al, 2005). Age definition of childhood was girls aged ≤14 years of age. The definition of adolescents used was girls aged ≥15 years and ≤19 years of age.

Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution (Segi, 1960). The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population averaged over the number of years for which data are presented'. Incidence tables were based on ICD-10 (WHO, 1992). Percent changes in pre- and postmenopausal rates over time reported were calculated. The cases were staged using the AJCC/UICC TNM system of staging. Data were analyzed using SPSS 19.0.

Results

Three hundred and thirty seven cases of ovarian malignancies were registered at the Karachi Cancer Registry (KCR) for the years 1995-2002. A hundred and thirty six cases were registered during period one (1995-1997) and two hundred and one cases were registered in period two (1998-2002). The age-standardized incidence rate (ASR) world per 100,000, crude incidence rate per 100,000 (CIR) and frequency of ovarian malignancies in period one were 10.9, 5.9 and 6.2% respectively.

Table 1. Distribution of Ovarian Malignancies by Age and Morphology (1995-2002)

| Morphology (ICD-O3)	Age (years) 1-14	15-19	20-44	45-64	65+	Total
Surface Epithelial-Stromal Tumors		3 (0.9)	101 (30.0)	129 (38.3)	34 (10.1)	237 (79.3)
Squamous cell carcinoma (M8070)			1 (0.3)			1 (0.3)
Adenocarcinoma, not otherwise specified (M8140)		2 (0.6)	28 (8.3)	29 (8.6)	11 (3.3)	70 (20.8)
Clear cell carcinoma (M8310)				2 (0.6)		2 (0.6)
Endometroid adenocarcinoma (M8380)			12 (3.6)	19 (5.6)	2 (0.6)	33 (9.8)
Serous adenocarcinoma (M8441, M8460, M8461)			37 (11.0)	64 (19.0)	11 (3.3)	112 (33.2)
Mucinous adenocarcinoma (M8470, M8471, M8480, M8490)	1 (0.3)		23 (6.8)	14 (4.2)	7 (2.1)	45 (13.4)
Adenosarcoma (M8933)					1 (0.3)	1 (0.3)
Mixed Müllerian tumor (M8950)				1 (0.3)	1 (0.3)	2 (0.6)
Brenner tumor (M9000)					1 (0.3)	1 (0.3)
Sex Cord-Stromal Tumors	1 (0.3)		6 (1.8)	6 (1.8)	2 (0.6)	15 (4.5)
Granulosa tumors (M8620)	1 (0.3)		4 (1.2)	6 (1.8)	2 (0.6)	13 (3.2)
Sertoli-Leydig cell tumor (M8631)			2 (0.6)			2 (0.6)
Germ Cell Tumors	9 (2.7)	10 (2.9)	12 (3.6)	1 (0.3)	1 (0.3)	33 (9.8)
Teratoma (M9080, M9082)	2 (0.6)	2 (0.6)	2 (0.6)			6 (1.8)
Dysgerminoma/germinoma (M9060, M9064)	5 (1.5)	4 (1.2)	7 (2.1)	1 (0.3)	1 (0.3)	18 (5.4)
Yolk sac tumor (M9071)	1 (0.3)	1 (0.3)	1 (0.3)			3 (0.9)
Mixed germ cell tumors (M9085)	1 (0.3)	3 (0.9)	2 (0.6)			6 (1.8)
Other, Specified Malignancies	1 (0.3)		2 (0.6)	2 (0.6)		5 (1.5)
Non-Hodgkins Lymphoma (M9675- M9687)	1 (0.3)		2 (0.6)	2 (0.6)		5 (1.5)
Other, Unspecified Malignancies			5 (1.5)	11 (3.3)	1 (0.3)	17 (5.1)
Total	11 (3.3)	13 (3.9)	126 (37.4)	149 (44.2)	38 (11.3)	337 (100)
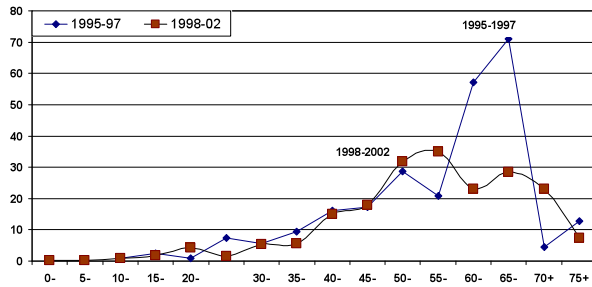
Figure 1. Age-specific Incidence Rates per 100,000

Corresponding figures for period two were 8.1, 5.1 and 4.8% respectively (Bhurgri et al, 2002; 2007).

In period one the mean age at presentation was 45.7 years (95%CI 42.9, 48.4; SD±15.9), range 95 years (3 to 98 years). Four (2.9%) cases were childhood cancers and 5 (3.7%) cases were observed in adolescents. Fifty three (39.0%) cases were observed in women aged between 19 and 44 years i.e. the reproductive age. Seventy four (54.4%) cases were registered in the peri and postmenopausal women (≥45 years). In period two (1998-2002) the mean age at presentation was 45.0 years (95%CI 42.8, 47.3; SD±16.1), range 79 (3 to 82) years. Seven (3.5%) cases were childhood cancers whereas 8 (4.0%) cases were observed in adolescents. Seventy three (36.3%) cases were observed in the reproductive and 113 (56.2%) in women above 45 years.

Age-specific incidence rates varied with tumor morphology, however the first cases were observed in infants (0-4 year age group) and a peak was observed in the 60-69 year age group (Figure 1). Epithelial malignancies were the most common cancers above the age of 20 years and the commonest amongst these was serous adenocarcinoma. Germ cell tumors were more common in the younger age groups, below 19 years of age (Table 1). Serous adenocarcinoma was twice as common as mucinous adenocarcinoma. There was one case of squamous cell carcinoma arising from mature cystic teratoma.

Microscopic confirmation was 99.0%. Overall presentation was of a moderately differentiated (grade 2) malignancy with a regional or distant spread of disease at diagnosis (Table 2).

Discussion

Ovarian cancers are the sixth most common cancers in females and account for approximately 4.0% of the cases

Table 2. Distribution of Ovarian Malignancies by Grade and Stage at Presentation (1995-2002)

		1995-1997 (n=136)	1998-2002 (n=201)
Grade	Well differentiated	13 (9.6)	74 (36.8)
	Moderately differentiated	64 (47.1)	76 (37.8)
	Poorly differentiated	47 (34.5)	43 (21.4)
	Unknown	12 (8.9)	8 (5.0)
Stage	Localized	35 (25.7)	63 (31.3)
	Regional spread	52 (38.2)	107 (53.2)
	Distant spread	42 (30.9)	28 (13.9)
	Unknown	7 (5.1)	3 (1.5)

in them (Parkin et al., 2005). In Asia, ovarian cancers are a relatively frequent malignancy, particularly in Pakistan (Moore et al., 2010). The incidence in Asia is relatively lower than in Europe and the United States (Edmondson and Monaghan, 2001; Parkin et al., 2002; Curado et al, 2007).

Karachi South an all urban population falls into a higher risk region for cancer ovary. The incidence is the second highest in Asia, after urban Delhi (Parkin et al., 2002). On a scale of 1-V as recommended by Globocan 2008 the incidence of ovarian cancer in Karachi South falls into the range of grade IV to V. Globocan (2008) estimates for country map Pakistan as a moderate risk country (grade III), similar to other regions in the Indian Subcontinent (Parkin et al, 2002; Curado et al, 2007; Ferlay et al., 2008).

In Karachi South cancer ovary accounted for 6.2% and 4.8% for the years 1995-1997 and 1998-2002. The malignancy ranked third, after breast and oral cavity cancers during the entire study period. Within Pakistan, there is a variation in the incidence of ovarian cancer, however most urban centers report it as the second or third commonest malignancy in females (Malik, 2002; Shahbaz Sarwar et al., 2006). Cancer ovary also features amongst the first three leading cancers in the metropolitan registries of India (Yeole et al., 2006; 2008a), though rural registries report a lower incidence (Mancharan et al., 2010).

The ASR world per 100,000 in Karachi South was 10.9 and 8.1 in 1995-1997 and 1998-2002 respectively (Bhurgri et al., 2005; 2007). The higher incidence of cancer ovary in Karachi South in 1995-1997 is likely to be an artifact, due probably to an over-registration of prevalent cases in the initial period of cancer registration. The next data set (2003-2008) would give more stable rates and a clearer picture of the true incidence in the population. Ovarian cancer incidence rates have been slowly increasing in many Western countries and Japan, whereas stables rates are reported elsewhere (Parkin et al., 2005 Yeole, 2008a; Day et al, 2010). In the United States, ovarian cancer incidence rates have remained constant for decades (Weiss et al., 1996). A slight increase in ovarian cancer incidence rates was observed in the 1980s, while between 1991 and 1998, a decline of about 1.1 percent annually was registered (Ries et al., 2001).

Ovarian cancer is a disease of increasing age (Edmondson and Monaghan, 2001). More than half (54%) of the KS cases were registered in the peri and postmenopausal women (≥45 years). The incidence remained low in the under-40 age group (39.7%). The maximum incidence was observed in the 65-69 year age group (Figure 1). This pattern is also reported from other regions of the subcontinent (Yeole et al, 2008b). In developed countries like the United Kingdom, with a higher life expectancy, the maximum incidence is observed in a much older age group (ASR 61.8 in the 80-84 year age group) (Edmondson and Monaghan, 2001). As the elderly population of Pakistan increases over the next few decades, we may observe a much higher incidence in the country.

The mean ages at presentation were 45.7 and 45.0 years. Large oncology-based hospital data have also reported a younger mean age (below 50 years) at

Table 4. Comparative Frequency of Ovarian Epithelial Malignancies in Pakistan

Morphological sub-type	Morphological Studies on Ovarian Carcinoma conducted in Pakistan				
	Muzaffar (1987)	Saeed (1991)	Ahmad (2000)	Sarwar (2006)	Bhurgri (2011)
Serous adenocarcinoma	27.6	27.5	33.3	28.6	33.2
Mucinous adenocarcinoma	48.3	25.0	15.7	13.4	13.4
Endometroid carcinoma	-	-	12.0	7.3	9.8
Total	75.9	52.5	61.0	49.3	56.4

presentation. Malik from Karachi in 2002 reported a mean age of 49.5 years whereas Sarwar from Shaukat Khanum Hospital, Lahore, in 2006 reported a mean age of 48.1 years. A mean age at presentation of 51 years was reported by Khan et al in 2010, from the gynecology department of a tertiary care hospital in Karachi. The Khan data is an all gynecological unit data and did not include non-gynecological unit childhood and adolescence ovarian cancers usually reported from the pediatric surgery or general surgery units, thus producing a selection bias. Approximately 7.2% of our cases were childhood and adolescence cases.

Tumor morphology varied with age in our series. Surface epithelial tumors were the commonest primary malignancies in adults above 20 years of age. Germ cell tumors were the most common childhood and adolescence ovarian cancers. These findings have been supported by other authors (Sarwar et al., 2006; Kayastha, 2009; Zaman et al, 2010). Serous cystadenocarcinoma was the commonest adult ovarian malignancy followed by mucinous adenocarcinoma, endometroid carcinoma, germinoma and mixed germ cell tumors, dysgerminoma, and granulosa cell tumor. A preponderance of serous cystadenocarcinoma (Table 3) has been reported by almost all authors in Karachi and Lahore (Muzaffar et al, 1987; Saeed et al, 1991; Ahmad et al, 2000; Malik 2002; Khan et al, 2010; Zaman et al, 2010). Sporadic studies of smaller number of cases from hospitals in Peshawar and Hyderabad have reported paradoxical data. Yasmin et al have reported granulosa cell tumors and endometriod carcinoma as the commonest ovarian cancers and Baloch et al in 2008 reported epithelial malignancies as the more common morphology in their series of adolescence ovarian tumors.

A case of squamous cell carcinoma (SCC) arising from mature cystic teratoma was also reported in a 40 year old woman. Ovarian SCC is a rare malignancy and the occurrence is attributable to malignant transformation of an existing ovarian dermoid cyst or may be a de novo occurrence (Amjad and Pal, 2008). SCC is the most common type of malignant transformation in mature cystic teratoma (MCT) and in a case series reported by Chiang et al in 2011, a median age of 39 years was reported.

The higher incidence of cancer ovary in Karachi is an enigma and belies the reproductive protective factors, like high parity (IARC Monographs, 1999). A family history was reported by a fourth of our cases, most of who presented at younger age. These concerns were also raised by Malik in 2002. Familial predisposition to ovarian cancer has been recognized for a long time (Edmondson and Monaghan, 2001), approximately 90% of familial ovarian cancers being attributable to mutations in the

BRCA1 and BRCA2 genes (Boyd, 2001). This may be a plausible reason for the higher incidence observed in KS. Rashid et al in 2006 have reported that BRCA1 and BRCA2 accounts for a substantial proportion of ovarian cancers in Karachi.

An advanced disease at presentation was observed by us. Only a third of our cases presented with localized disease, whereas two thirds presented as a regionally spread disease or were diagnosed with distant metastasis (table 3). This has earlier been reported by other authors in Pakistan (Malik, 2002; Sarwar et al., 2006)

In conclusion, the incidence of cancer ovary though stable in Karachi, involves a relatively younger age group with a strong family history in a fourth of the cases. The disease presents at an advanced stage. An ageing population over time may translate into a higher incidence of ovarian cancer. The current incidence of cancer ovary in Karachi is an enigma and belies reproductive protective factors. Studies focused on the genetic risk factors in this population are recommended.

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