RESEARCH COMMUNICATION

Patho-epidemiology of Breast Cancer in Karachi '1995-1997'

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Abstract

Objective: Provide an overview of the demographics and pathology of breast cancer in the female population of Karachi South during a 3 year period, 1995-1997. Methods: Epidemiological data for 709 incident breast cancer cases, ICD-10 category C50 registered at Karachi Cancer Registry during 1st January 1995 to 31st December 1997 were reviewed. Results: Breast cancer accounted for approximately one-third of the cancers in females. The age standardized incidence rate (ASR) world per 100,000 was 53.8, the crude incidence rate was 30.9. In KS 60% of the newly diagnosed breast cancers were observed in women below 50 years. The age-specific curves showed a gradual increase in risk from the third up till the seventh decade, followed by an actual/apparent decrease in risk. The socio-economic distribution was 24.9% in category I the financially deprived class, 38.9% in category II the middle class and 35.9% in category III, the affluent class. Microscopic confirmation of malignancies was 99%. Invasive breast cancers predominated with 99.4%, with in-situ cancers contributing to 0.6% of the malignancies. The morphology of cancers was tilted towards duct cell carcinoma (DCC), pure DCC (92%), combinations of DCC /Paget's disease (0.6%) and lobular carcinoma (0.4%). Approximately 45% of duct cell carcinoma were seen in the premenopausal age group (<45 years). All bilateral breast cancers were duct cell carcinoma with a family history of first degree relative with breast cancer. The majority of the cases presented as moderately differentiated or grade 2 lesions (59.0%). Approximately 56% cancers had spread to the regional lymph nodes and 8.3% to a distant site at the time of diagnosis. A family history of first degree relative with breast cancer was present in 3% and second degree relatives in 7% of the cases. Odds ratio (OR) for 680 breast cancer cases with complete demographic information was calculated with 675 gender matched controls. A slightly higher risk was observed in non-Muslims and migrant ethnicities: two to three fold elevation in the Indian migrants (Gujrati speaking Mohajirs OR 3.86 (95% CI 2.51; 5.92) Urdu speaking Mohajirs OR 2.85 (95% CI 2.05; 3.96), Memon Mohajirs OR 2.21 (95% CI 1.48; 3.29) and Afghan migrants [OR 2.99 (95% CI 11.20; 7.44)]. The risk was also high in the females of Punjabi ethnicity settled in KS [OR 2.73 (95% CI 1.87; 3.99)]. The risk seems much less for the ethnicities belonging to North Western Pakistan i.e. Pathans [OR 1.684 (95% CI 0.89; 3.17)] and Baluchs [OR 0.90 (95% CI 0.58; 1.39)]. A marginally higher risk was observed in the higher socio-economic categories.The risk of developing breast cancer increased gradually for each age category from illiterate [OR 1.2 (95% CI 0.94; 1.55)] to college graduates [OR 13.12 (95% CI 7.31; 23.73)]. Conclusions: The incidence of breast cancer in Karachi South (KS) for the period 1995-1997 was the third highest in Asia. The hallmarks were a high reproductive age malignancy involving a higher socio-economic class, an invasive duct cell carcinoma diagnosed at an advanced stage, in younger more educated females and a low in-situ malignancy. More studies are required to obtain a deeper insight into this breast cancer epidemic in Karachi. Implementation of breast cancer screening with stress on public health education is today a major responsibility of the government.

Key Words: Breast cancer - Karachi, Pakistan - pathology - ethnic and socioeconomic background

Asian Pacific J Cancer Prev, **8**, 215-220

Introduction

Cancer breast ICD-10 category C50 (International Classification of Diseases 10th Revision) is the most common malignancy in women in both developing and developed countries and also the principal cause of cancer death among women globally (Bray et al., 2004). It is three times more common than all gynecologic malignancies put together and the incidence is increasing unabated. In the year 2000, of the estimated 10 million

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new cancer cases, breast cancer accounted for 1.05 million, i.e. one in ten of all new cancers diagnosed (Parkin 2004; Bray et al., 2004).

Cancer breast is not a disease of modern times as it was documented by Ancient Egyptians as early as 1600 BC in the Ebers" papyrus as cited by Sameh Arab in Medicine in Ancient Egypt. Over the last 50 years however, it has become a major health problem reaching epidemic proportions and affecting as many as one in eight women during their lifetime (Sondik, 1994; Ries et al., 1999). Breast cancer has a global distribution with a wide variation in its biological behavior. It is a different disease in different populations, in different women in the same population, in different age groups, and may have a different cell population within the tumor itself. In 'Cancer in the Five Continents', eighth volume (CIV-8) the age-standardized incidence rates (ASRs) per 100,000 population for breast cancer in females varied from the lowest (8.6) in Gambia to the highest (97.9) in Atlanta, Georgia for the same time period (1993-1997) (Parkin et al., 2002).

An increasing incidence has been reported globally for breast cancer which is a significant health problem in the industrialized western world. In the United States (US), for instance, the incidence has increased steadily by about 1–2% per year since 1960, though a decrease is being reported in the recent years (Lynn et al., 1995; Hortobagyi and Buzdar, 1995; Forbes, 1997; Ravdin et al., 2007). The incidence in Asia and Africa is considerably lower than in North America and Europe. In Japan and other Far Eastern countries, the increase in incidence with age seen elsewhere in the world is mirrored, but absolute rates of incidence are lower for each age band; Japanese women are five times less likely to develop breast cancer than American women. Japanese immigrants to the US lose this advantage within 1–2 generations, assuming the same risk profile as American women. This observation suggests that environmental factors play a role in developing the disease. Figures from epidemiological studies also indicate that the risk advantage demonstrated by native Japanese women may be dissipating; with the incidence of breast cancer in Japan doubling between 1960 and 1985 (Nagata et al., 1997). This change in the prevalence of the disease may reflect the increasing adoption of Western lifestyles in Japan over the last 50 years.

In Pakistan, breast cancer is the most frequent malignancy of women as reported from all regions of the country, Arabian Sea upto the Himalayas (Bhurgri et al, 2005; 2006a; 2006b). The only exception is the esophageal cancer belt in the Baluchistan Plateau, in the northwest of Pakistan (Bhurgri et al., 2002; 2006b). In Karachi, it accounts for approximately one-third of the cancers in the females.

The incidence of breast cancer in the Karachi females is one of the highest in Asia for this period (Bhurgri Y et al, 2000). The ranking order of cancers following breast cancer, for the years 1995 – 1997 was oral cavity ICD-10 categories C00-08 (ASR 15.5/100,000), ovary ICD-10 category C56 (ASR 10.9/100,000), uterus ICD-10 categories C54-C55 (ASR 7.2/100,000), esophagus ICD-10 category C15 (ASR 6.9/100,000), cervix ICD-10 category C53 (ASR 6.8/100,000), colo-rectum ICD-10 categories C18-20 (ASR 5.5/100,000), gall bladder ICD-10 category C23 (ASR 5.3/100,000), skin ICD-10 category C44 (ASR 4.9/100,000), lymphoma ICD-10 categories C81-85; C96 (ASR 4.4/100,000); and thyroid ICD-10 category C73 (ASR 4.2/100,000).

The present study was conducted with the objective of examining descriptive epidemiological characteristics and pathology characteristics of breast cancer and to obtain a deeper insight into the breast cancer epidemic in Karachi.

Patients and Methods

Epidemiological data of incident breast cancer cases, ICD-10 category C50 registered at KCR for Karachi South, during 1st January 1995 to 31st December 1997 were reviewed. The study included clinically diagnosed and microscopically verified breast cancer cases. All surgical specimens were initially evaluated on Hematoxylin and Eosin (H&E) stained sections and subsequently immunohistochemical analysis was performed to determine the estrogen and progesterone receptors status. Special stains were selectively used, whenever required. The reported epidemiological cancer data were rechecked, and residency status re-ascertained. People residing in the specified geographical regions for more than six months were considered residents. The cases were categorized by tumor site, age and sex of the patient. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, ER/PR status, grading and staging. The data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-4 software. This software includes facilities for the detection of duplicate registrations and for performing internal checks on the validity of the entered data. Manual and computerized validity check for the cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR). This involved factors influencing comparability i.e. classification and coding (Parkin, 1994). Tumors were categorized by morphology types and graded by the Richardson Bloom system to standardize with other parts of the world. The Bloom-Richardson grading scheme is a semi-quantitative grading method based on three morphologic features of invasive (no-special-type) breast cancers, the degree of tumor tubule formation, tumor mitotic activity and nuclear pleomorphism of tumor cells.

Crude, age-adjusted, and age-specific incidence rates were calculated for breast cancer in females. The person-years of population at risk by sex and 5-year age-groups were estimated with the mid 1996 population, based on the 1998 census (copy obtained from the Sindh Bureau of Statistics), population of 1,724,915; females 795,521, assuming an annual growth rate of 1.94%. The growth rates were based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age

distribution (Segi M, 1960). 'The standardized rate is the incidence rate that, theoretically, would have been observed if the population had a standard age distribution. 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).

To determine the socioeconomic profile, the district was divided into 3 subcategories based on the income of approximately 70% of the resident population. The categories ranged from 1 to 3 in an ascending income strata (Table 1). Category I was composed of the predominantly financially deprived class with an annual income of less than $2000, and a low literacy level. Residents of category II had an annual income range of $2001-$20,000 with a moderately high literacy. Category III was largely made up of educated professionals, with an annual income of more than $20,000. A sample survey was conducted to categorize the financial status of the population.

Odds ratio for sex, age-groups, ethnicity, religion, and subdivision by socio-economic categories were calculated by considering all malignancies in females, ICD-O3 morphological categories less than and excluding M-8140 and reproductive system malignancies for the same period (1st January 1995 to 1st December 1997) as controls. The data were analyzed using SPSS 13.0.

Results

A total of 709 cases of breast cancer, ICD-10 (International Classification of Diseases 10th Revision) category C50 were registered at the Karachi Cancer Registry, for Karachi South, during a 3 year period, 1st January, 1995 to 31st December 1997. The age standardized incidence rate (ASR) world per 100,000 was 53.8 (48.89, 57.37), the crude incidence rate per 100,000 was 30.9.

Twenty nine cases were notifications without any additional information except the gender and malignancy. These cases were excluded from all analyses except the calculation of the incidence rates. Thus 680 cases were included for further analyses. The mean age of the cancer patients was 47.5 years (95% CI 46.49; 48.52). The age range was 79 years (minimum 16 years; maximum 95 years). The mean age of in-situ cancer cases was 59.0 years (95% CI 38.66; 79.34) with an age range of 29 years (minimum 43 years; maximum 72 years). The mean age of invasive cancer cases was 47.44 years (95% CI 46.41; 48.46). The age range was 79 years (minimum 16 years; maximum 95 years).

The age-specific curves showed a gradual increase in risk from the third until the seventh decade, followed by an actual apparent decrease in risk. The distribution by religion was Muslims (94.1%), Christians (2.6%), Hindus (2.1%), Parsees (1.0%) or other religions (0.1%). The frequency distribution by ethnicity is given in Table 1, along with data for education and economic status. Married women formed 86.9%, divorcees 4.9% and unmarried females 6.0% of the total number of cases. The marital status was not known in 1.9% of the cases. Housewives formed the bulk of the cases (94.4%), whereas working women were only 5.6% . The professions followed were teaching (0.7%), office workers (0.6%), medicine (1.9%) and household workers (1.8%). The profession was not known in 0.6% of the cases.

Table 1. Frequencies and Odds Ratios of Breast Cancer Cases on the Basis of Age-group, Socio-economic Categories, Religion, Ethnicity and Education

Age groups	Number	Frequency %	OR*	CI#
0-4	-	-	0.0	-
5-9	-	-	0.0	-
10-14	-	-	0.8	0.17; 3.28
15-19	3	0.4	1.5	0.54; 4.37
20-24	10	1.5	1.8	0.76; 4.37
25-29	21	3.1	4.5	2.02; 9.84
30-34	58	8.5	4.1	1.92; 8.53
35-39	81	11.9	3.4	1.71; 6.93
40-44	136	20.0	2.2	1.10; 4.50
45-49	87	12.8	1.6	0.80; 3.32
50-54	77	11.3	2.4	1.15; 5.10
55-59	63	9.3	1.2	0.60; 2.50
60-64	55	8.1	1.2	0.50; 2.50
65-69	31	4.6	2.2	0.92; 5.24
70-74	21	3.1	0.7	0.31; 1.55
75-79	23	3.4	2.1	0.92; 5.24
80+	14	2.0	1.0	
Socio-economic categories				
Unknown	2	0.3	1.0	
Category I	169	24.9	0.55	0.42; 0.72
Category II	265	38.9	0.95	0.73; 1.23
Category III	244	35.9	1.25	0.70; 1.7
Religion				
Muslim	640	94.1	0.79	0.07; 1.52
Non-muslim	40	5.9	1.20	0.18; 2.2
Ethnicity				
Unknown	116	17.1	1.00	
Sindhi	45	6.6	1.48	0.94; 2.33
Punjabi	102	15.0	2.73	1.87; 3.99
Pathan	21	3.1	1.68	0.89; 3.17
Baluch	41	6.0	0.90	0.58; 1.39
Mohajir (u)	173	25.4	2.85	2.05; 3.96
Mohajir (g)	90	13.2	3.86	2.51; 5.92
Mohajir (m)	79	11.6	2.21	1.48; 3.29
Afghanis	13	1.9	2.99	1.20; 7.44
Education				
Illiterate	266	39.1	1.21	0.94; 1.60
Literate	92	13.5	3.66	2.40; 5.57
Primary	16	2.4	3.18	1.33; 7.60
Secondary	8	1.2	6.36	1.33; 30.3
High school	21	3.1	8.35	2.81; 24.76
Graduation	116	17.1	13.18	7.31; 23.73
Unknown	161	23.7	0.63	

*Odds ratios, #95% Confidence Intervals

Microscopic confirmation of malignancies was 99%. Invasive breast cancers predominated with 99.4%, with in-situ cancers contributing to 0.6% of the malignancies. The morphology of cancers was duct cell carcinoma (M-8500/3, M-8500/2; 92.0%) and combinations of duct cell carcinoma with other tumor types viz. infiltrating duct cell carcinoma and Paget's disease (M-8541/3; 0.6%), infiltrating duct cell and lobular carcinoma (M-8522/3;

0.4%). Other categories which formed a minor component were medullary carcinoma (M-8510/3; 1.6%), lobular carcinoma (M-8520/3; 1.0%), malignant Phylloides (M-9020/3; 0.7%), intraductal papillary carcinoma with invasion (M-8503/3;0.6%), mucinous adenocarcinoma (M-8480/3), non-infiltrating intraductal papillary adenocarcinoma (M-8503/2) 0.4% each, comedocarcinoma (M-8501/3; 0.3%), squamous cell carcinoma (M-8070/3), adenocarcinoma é neuroendocrine differentiation (M-8574/3), Granular cell carcinoma (M-8320/3), non-Hodgkins Lymphoma (M-9680/3) and metaplastic carcinoma (M-8575/3) 0.1% each. Morphological sub categorization was not possible for 1% of the cases. Breast cancers arising in females below 30 years of age were mostly duct cell carcinoma with 2 cases of malignant Phylloides. Approximately 45% of duct cell carcinoma were seen in the premenopausal age group (<45 years). All bilateral breast cancers were duct cell carcinoma with a positive family history of breast cancer.

The majority of the cases presented as moderately differentiated or grade 2 lesions (59.0%), whereas well differentiated (grade 1), poorly differentiated (grade 3) and anaplastic or undifferentiated malignancies formed 19.9%, 10.6% and 0.3% of the cases respectively. The tumor grade was not known for 10.3% of the cases. In almost two-thirds of the cases, breast cancer was discovered at advanced stages. Approximately 56% cancers had spread to the regional lymph nodes and 8.3% to a distant site at the time of diagnosis. Localized cancer was observed in 28.1% of the cancers. The left breast was affected in 42.4%, the right side in 38.6% and both breasts 1.5% of the cases. Laterality was not known in 17.6% of the cases. A family history of breast cancer is noted in approximately 3% of the cases registered. A family history of first degree relative with breast cancer was present in 3% and second degree relatives in 7% of the cases.

The odds ratio (OR) for 680 cases was calculated with 675 gender matched controls. The odds ratios were calculated for socioeconomic residential categories, religion, ethnicity, age groups and education. The OR for socioeconomic residential categories ranged between 0.55 and 1.3 with a marginally higher risk in the higher socio-economic categories. Non-Muslims had a slightly higher risk then the Muslims. A higher risk was also observed for migrant ethnicities. The risk of developing breast cancer two to three fold in the Indian migrants and Afghan migrants. The risk was also high in the females of Punjabi ethnicity settled in KS. The risk seems much less for the ethnicities belonging to North Western Pakistan i.e. Pathans and Baluchs.

The highest risk of breast cancer was observed in the 25-39 years of age i.e. the reproductive age group as compared with the control group. A five fold risk was seen in the 25-39 years age group; a four fold risk in the 30-34 year age group and a three fold risk in 35-39 years age group. The risk of developing breast cancer increased gradually for each category from illiterate to college graduates.

Discussion

The incidence of breast cancer in Karachi South (KS) for the period 1995-1997 was the third highest in Asia. The hierarchy of breast cancer incidence (ASR/100,000) in Asian registries for the 1993-1997 period as reported in CIV-8 was Jews born in Israel (91.2), Philippines, Manila (58.0), KS (53.8), Philippines, Rizal Province (45.9), Singapore: Chinese (44.7), Singapore: Malay (37.2), Singapore: Indian (36.7), China: Hong Kong (36.3), Kuwait: Non-Kuwaitis (35.1), India, Mumbai (30.1). These rates are much lower than the incidence of breast cancer in the United States and Europe. Comparative contemporary (1993-1997) rates in the US for female breast, SEER white were 92.4/100,000 (Parkin et al., 2002).

Age standardized incidence for breast cancer varies by up to a factor of five between industrialized countries of North America and Europe and the Asian countries (McPherson K et al, 2000). The difference between US SEER and selected Asian populations is Seoul, Korea (4 fold), Japan, Hiroshima and India, Bombay three fold each. The difference between US SEER and Karachi South is only two fold, indicating a much higher risk in Karachi in comparison to other Asian countries (Parkin et al, 2002).

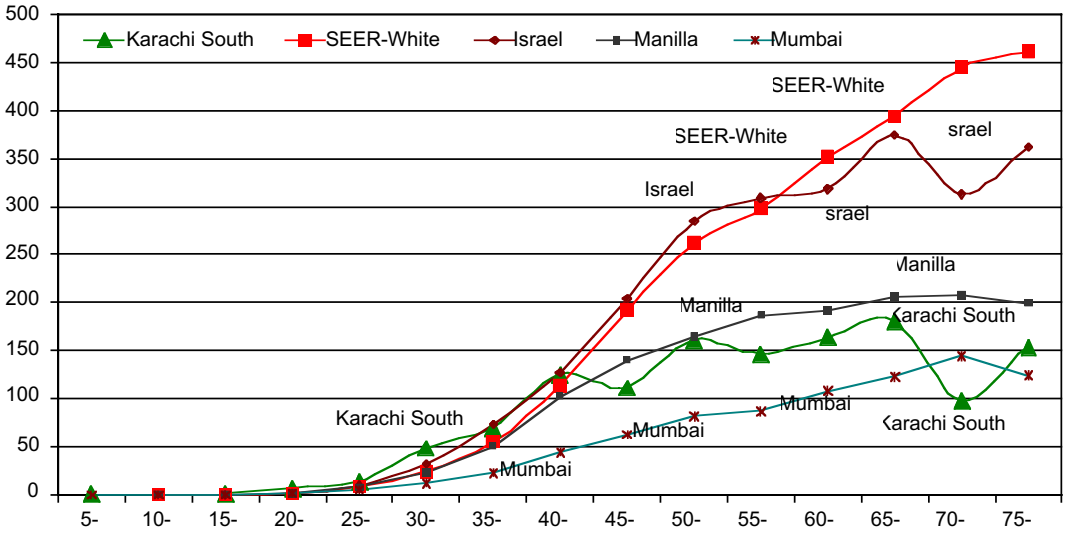

Figure 1. Comparison of Age-dependent Breast Cancer Incidences in Different Registries

The mean age of breast cancer cases was 47.5 years in KS. This finding is compatible with reported studies from Bombay (Badwe et al., 1990). The incidence of breast cancer in younger women or breast cancer of reproductive ages in KS is the highest reported globally. In KS 60% of the newly diagnosed breast cancers are observed in women below 50 years as compared to only 25% in the US (Sondik, 1994; Ries et al., 1999). In KS for all ethnicities combined, women aged 20-24 had an ASR per 100,000 of 14 and women aged 75-79 had an ASR per 100,000 of 153.1. In contrast the contemporary (1994-1998) US, ASR per 100,000 was only 1.5 in women aged 20-24 and 489.7 for women aged 75-79, though Black women in the US under age 40 had a slightly higher incidence than white women. (Ries et al., 2001). Up till the age of 40 years the incidence rates in Israel and Manila also remain relatively below than the rates of KS. After the age of 40 years the ASIRs in Israel rise dramatically whereas there is a flattening of the age-incidence curve for Manila and Karachi South. The Indian cancer registries show overall lower breast cancer rates as well as lower ASIRs for all age groups. Figure 1 highlights the age specific incidence rates in Karachi South in comparison to some selected Asian registries as well as SEER whites (Parkin et al., 2002).

The incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically (McPherson et al., 2000). In KS the incidence of breast cancer multiplied 12 times between 15 to 20 years and 5 times between 25 to 35 years. From 35 years to 45 years the rate of increase had fallen to 1.6 fold, between 45 and 55 years to 1.3 fold. This indicates that there is a dramatic rise in the incidence of breast cancer in the younger age groups (15 to 35 up till 45 years) in this population.

Late presentation remains a hallmark of breast cancer in Karachi, with 63% of the cases being discovered at advanced stages (III and IV). This figure is much higher than the stage at diagnosis reported for India (50-55%) and the US (15%) (Hebert et al., 2006). The low incidence rates of in situ breast cancers in KS, reflect the lack of screening. In the US the increase observed over the past 25 years is mostly due to detection of ductal carcinoma in situ (DCIS) with mammography. From 1994 to 1998 DCIS accounted for 51% of the in situ breast cancers diagnosed among women in SEER areas as compared with 0.6% in KS. The mean age of in-situ cancers was 12 years more than the invasive cancers, and all were detected incidentally in a background of adenosis in symptomatic females, as screening has not been implemented in the country.

Non-Muslims, Parsees, Christians and Hindus in the order of hierarchy had a slightly higher risk then the Muslims. Jussawalla et al in 1981 had also reported a higher incidence of breast cancer in the case of Parsees and Christians in Bombay. The numbers of the non Muslim cases in our study were much smaller than the Muslims, thus the data needs careful interpretation. The preponderance of educated women with breast cancer has also been observed in Bombay (Kurkure and Yeole, 2006).

The accepted risk factors for breast cancer include genetic and environmental categories. Age at menarche and menopause, age at first pregnancy, previous benign breast disease, and lifestyle risks related to diet, weight, alcohol intake, smoking, oral contraceptive, hormone replacement therapy. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance. This means that it can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves. It is not yet known how many breast cancer genes there may be. Two breast cancer genes, BRCA1 and BRCA2, which are located on the long arms of chromosomes 17 and 13 respectively, have been identified and account for a substantial proportion of breast cancers (McPherson et al., 2000).

In our population reproductive factors cannot be considered a major risk factor as early marriages, multiple births and prolonged breast-feeding are the norm. Early menarche, late menopause and thus the prolonged effect of reproductive hormones could however be possible risk factors along with dietary factors and obesity. In KS a family history of first degree relative/s with breast cancer was present in 3% of the cases and 10% in second degree relatives. This coincides with genetic predisposition of up to 10% reported for Western countries (McPherson et al., 2000). All cases of bilateral breast cancers had a strong family history of breast cancer. Patients with bilateral breast cancer are most likely to be carrying a genetic mutation that has predisposed them to developing breast cancer.

The roles of BRCA1, BRCA2 and other genetic factors have not been adequately studied in this population. A recently published study has reported thirty deleterious germ-line mutations in the 176 families (17.0%), including 23 in BRCA1 and 7 in BRCA2, four recurrent mutations, 185delAG, 185insA, S1503X and R1835X accounting for 52% of all identified BRCA1 mutations. (Rashid et al., 2006) Another study has confirmed substitution of thymine at position 1123 with guanine of exon 11 (1123 T>G) in a case of medullary carcinoma with a family history (Moattar et al,. 2006).

The incidence of breast cancer varies by race and ethnicity. Though there are claims of high breast cancer incidence from all regions of the country (Aziz, 2003), the rates of Karachi South should not be generalized as the population of Pakistan has a wide ethnic variation. Ethnicity plays a role in the risk of developing breast cancer. Although breast cancer remains the leading cancer in black women in the US, overall they have an incidence rate nearly 20% lower than that of American white women (Sondik, 1994).

To concclude, the hallmarks of breast cancer in Karachi South (KS) for the period 1995-1997 were a high incidence rate for Asia, a high reproductive age malignancy involving a higher socio-economic class, an invasive duct cell carcinoma diagnosed at an advanced stage and in younger females and a low in-situ malignancy. More studies are now necessary to obtain a deeper insight into this breast cancer epidemic in Karachi. Breast cancer screening and public health education are urgent requirements..

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