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LIFE STYLE CHARACTERISTICS: RISK FACTOR FOR BREAST CANCER

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ABSTRACT

The purpose of this study was to identify various life style risk factors of breast cancer in Pakistani females. This was an observational case control study. The breast cancer cases (n= 811) were from KIRAN hospital, Karachi and the control group (n= 1154) was population based, also from Karachi city. A researcher administered questionnaire was used with face to face interviews with the study subjects, from April 2011 to April 2012. The data was analyzed using SPSS version 16.0. Mean age of the control group was 45.85±9.97 years and that of the breast cancer cases was 47.02± 11.79 years. More than 90% females were housewives (p=0.002) among which more than 50% had interfamily marriage (p<0.001). Only 30% controls and about 60% cases consumed milk regularly (p<0.001) with majority consuming fresh milk (p<0.001). The family history of breast cancer was found in 15.65% cases only (p<0.001). From binary logistic analysis it was seen that odds were higher for developing breast carcinoma regarding interfamily marriage (p<0.001), housewives (p=0.003) and regular milk consumption (p<0.001). The odds were much higher for illiterate subjects (p<0.001) and in those having concomitant hypertension and diabetes mellitus (p<0.001). Bivariate adjusted models in logistic regression analysis also revealed higher odds regarding these factors for the attainment of breast carcinoma; multivariate logistic regression analysis further supported that specifically interfamily marriage and regular milk consumption had much higher odds for the development of breast cancer. The results have revealed various life style factors that are potential risk for the development of breast carcinoma in the Pakistani females and these risk factors may vary worldwide due to environmental and cultural disparities; hence very important in detecting specific population at risk of breast cancer.

KEY WORDS: Breast cancer, risk factors, life style characteristics.

INTRODUCTION

The incidence of breast carcinoma has augmented universally with time [1] (Hery et al., 2008) . This increase in the occurrence of breast cancer has been found in developing countries worldwide which may be due to the increased accessibility of healthcare settings that help in the diagnosis of the ailment [1]. The forms of breast cancer are complicated and multifarious than its occurrence [2,3]. Breast malignancy is also the most prevalent cancer in Asian females and its incidence has been rising in Asia [4]. The occurrence of breast malignancy in Pakistan is on top in Asia after Israel and 2.5 times higher than that in some nearby countries, accounting for 34.6% of female cancers [5]. Scarce information regarding breast cancer etiology and epidemiology in Pakistan necessitates awareness and investigation about its susceptibility factors in the inhabitants so as to avert or treat and decrease its frequency. The Western system of living is unlike that of Pakistani communities; thus all the globally well-known risk factors of breast cancer are not valid here and need to be studied statistically to understand its incidence.

The risk factors associated with breast cancer have been considered and identified in various studies [6,7]. Occurrence of breast cancer differs according to genetic, reproductive as well as cultural, environmental and life-style aspects; it also differs due to diversity of these factors within miscellaneous ethnicity and geographical zones. This acmes the massive requirement for such studies in all varied populations [5, 8, 9].

Age has been considered as the solidest recognized risk factor for breast malignancy in females; its relationship with breast cancer is described to be lesser in the younger age but it then rises as the age is more than 40 years [10]. Body mass index has been linked with escalated breast cancer risk, principally in postmenopausal women [11,12]. Obesity in post menopausal women has been identified to enhance both breast cancer risk and mortality [13,14]. Some researches

have shown shielding effect for breast cancer due to exercise [15].

The education level and SES (socio economic status) have been defined as significant aspects to the occurrence of breast cancer. It has been seen that lower education level and low SES promote patient delay at the healthcare facilities for seeking medical support [16]. The females who are educated and belong to a relatively higher SES have found to have more access to healthcare facilities and hence are recognized to be connected with breast cancer [17,18]. This has added in the diminution of mortality rates of breast cancer due to early identification and timely start of the management [19,20].

It has been proven that only 10% of breast carcinoma are due to genetic causes and family history of the disease has been acknowledged as a strong risk factor[10,21]. In a recent study it was revealed that the odds ratio for first degree family history of breast cancer was established as strong for younger females than older ones and also statistically important [22]. Consanguineous marriages are common in Pakistan [23,24]. In Pakistan, the apparent reasons for its high breast cancer incidence in spite of much of consanguineous marriages could be a tiny account of consanguinity and gene inferences. The information about social and population immigration records may increase data clarification. Yet, consanguinity should be taken as a possible risk factor for breast carcinoma which may also elucidate worldwide distinctions in breast cancer occurrence [25].

There are no well-known confirmations for strong associations of diet and smoking with breast carcinoma [10,26]. From a meta-analysis regarding meat consumption it was seen that the RR (relative ratio) of breast carcinoma was 1.17 when compared with highest and lowest levels of consumption [27]. Mahoney et al., (2008)[28] acknowledged that the existence of antioxidants and fibers in fruits and vegetables could not show any shielding effects against breast malignancy for those consuming in their diet. The intake of dairy products has shown varying patterns of relationship as risk for breast malignancy. Due to evidence of existence of pesticides and insulin growth factor I, milk and cheese have been reported to be connected with breast cancer [29]. A high alcohol ingestion relates to a mild but high breast cancer risk [26]. It was also observed in a recent study that ER+ and PR+ breast carcinoma are more related with alcohol ingestion than any other forms of cancers [30].

The xenoestrogens (exogenous estrogen or estrogen like compounds) can be linked with breast carcinoma when they come in contact with breast cancer cell lines [31,32,33]. Numerous such xenoestrogens have been found to act via estrogen receptor[34,35]. There are so many chemicals that interfere with hormonal metabolism for example dichlorodiphenyltrichloroethane (DDT), polyvinyl chloride (PVC) and polychlorinated biphenyls (PCBs) that are widespread in plastics, detergents, food containers, different pesticides, etc. [36]. Polycyclic aromatic hydrocarbons (PAHs) are chemical oncogenic agents that are formed due to partial combustion of organic materials and there are a lot of sources for PAHs in environment i.e. air pollution, tobacco smoke, wood- and coal-burning stoves, etc. [37]. All PAHs do not have the capability to cause similar grade of cancer which is due to variability in their structure and biological activity. PAHs fix to DNA and are often deposited in adipose tissues and fatty tissues of the breasts [38,39]. Smoking is known to have an undefined connection with breast cancer risk specially for genetically susceptible individuals [40,41]. Only a mild positive and statistically significant association between passive (second hand) smoking and breast cancer risk has been identified [42,43].

The use of exogenous hormones (i.e. contraceptives and hormone replacement therapy) has also been found to be related with breast cancer [10]. The use of contraceptives for ≥5 years has been found linked with breast cancer among younger females especially with ER- and triple negative breast cancer but this needs more investigation for validation [44]. It was reported in a study with postmenopausal females that due to use of HRT (estrogen plus progestin) females had a 5-6% greater risk of breast carcinoma [45]. An amplified risk of breast cancer has been identified in females with higher level of education due to use of these exogenous hormones [46].

Diabetes mellitus and hypertension have emerged as main health alarms globally. Almost 285 million people suffering from diabetes internationally were reported in 2010 demonstrating a frequency of 6.4% [47]. Hyperinsulinaemia is an indicator of insulin resistance in obesity and type 2 DM and has been regarded as a probable reason in attainment of breast carcinoma [48,49]. Hyperinsulinaemia may also have joint effects with the insulin growth factor I that could elaborate breast cancer-causing developments [50]. Insulin is also recognized as a growth- supporting hormone in-vitro with mitogenic effects in both normal and malignant breast tissues [51,52]. It is also reported that chronic hyperglycaemia might promote breast cancer risk via Warburg effect, in which cancerous cells principally yield energy by a high level of glycolysis in the cytosol [53,54]. Largent et al (2006)[55] performed a case-control study among post-menopausal women aged 50-75 years to study the relationship of breast cancer risk with hypertension and anti hypertensive drugs. They found that the history of cured hypertension was related with considerably greater breast cancer risk but only in the females with BMI ≥25 kg/m^2. Diuretic use was also linked with greater risk of breast malignancy which rose with time period of its use while the use of other antihypertensive drugs was not recognized to be associated with breast cancer risk.

METHODOLOGY

This research is observational, non interventional and case control study. The breast cancer cases were taken

from KIRAN hospital, Karachi and the control group was population based from Karachi city. The study was accomplished on researcher administered questionnaire and face to face interviews with the study subjects. The data of the study subjects was collected from April 2011 to April 2012. The subjects employed for this study were adult Pakistani females. The study participants were informed well about the purpose of this study and their consents were also obtained prior to the study. There were n= 811 breast cancer cases and n= 1154 controls in this study. Mean age of the control group was 45.85±9.97 years and that of the breast cancer cases was 47.02± 11.79 years.

The questionnaire was pre-tested to confirm the information required for this study and was then modified accordingly. The interview was directed to determine information regarding marital status, interfamily marriage, education, any concomitant disease, family history of breast cancer, some life style characteristics (i.e. eating betel nuts or betel leaves, milk consumption, tea consumption and diet).

After completing the questionnaires for both the controls and the cases of breast cancer, the data collected was coded and entered in the computer system. Some data was based just on dichotomous replies (yes/no); however, some questions were complex and their responses were classified and coded. At first all the categorical and continuous variables were determined to perceive the general data pattern, starting with descriptive statistics. Then, logistic regression was also used for further analysis. The results of the statistical analysis were confirmed by an expert statistician. SPSS version 16.0 was employed for data analyses. The initial data generated significant statistics and the data displaying extreme values were let off to evade distortion in the analysis.

RESULTS

The study population comprised of n= 811 breast cancer cases and n= 1154 controls (total=1965 subjects). Mean age of the control group was 45.85±9.97 years and that of the breast cancer cases was 47.02± 11.79 years. Fig. 1 shows the age distribution among the controls and cases of breast cancer. and Fig. 2 shows the percentage of working women and housewives in the controls and cases revealing that majority were housewives (>93%).

The socio-demographic characteristics using descriptive statistics for controls and cases of breast cancer are shown in Tables 1 and 2 for frequency and percentages. It can be seen that most of the subjects had age group of 41-50 years ($p=0.02$), were housewives ($p=0.002$) with no interfamily marriage ($p<0.001$). Most of the cases were illiterate (40%) and primary education was sought by about 28% subjects ($p<0.001$). More than 50% cases were regular fresh milk users ($p<0.001$) while > 85% subjects consumed tea on regular basis ($p=0.003$). More than 50% subjects consumed vegetable diet ($p<0.001$). From Table 3 it can be seen that only approximately 15% cases had family history of breast cancer; mostly in sister or paternal relative ($p<0.001$). More than 60% subjects had no concomitant disease and about 16% were suffering from hypertension ($p=0.001$).

Binary univariate logistic regression was applied to estimate the odds (with 95% C.I.) of various risk factors of breast cancer in controls and cases as shown in Tables 4 and 5. The odds were infinite for the history of breast cancer in the family among subjects, hence could not be mentioned. The odds were higher for the housewives and interfamily marriage for attainment of breast cancer (Table 4); the odds regarding education kept on rising towards very higher side as the education level of the subjects went down. Although hypertension and diabetes mellitus individually have shown higher odds for breast cancer risk but these two ailments together showed more risk for attaining breast malignancy (Table 4). Regular milk consumption, whether fresh or pack, have showed higher odds for attaining breast cancer while diet showed protective effects regarding breast cancer risk (Table 5).

A series of adjusted bivariate and multivariate logistic regression analyses models were then applied including all variables of interest related to breast cancer risk. Odds were estimated with 95% C.I. (Tables 6-8). It was revealed that being housewife with interfamily marriage, lower education levels, concomitant hypertension+diabetes mellitus and regular use of milk (both fresh and pack) were associated with higher risk of breast cancer (Tables 6 and7). Table 8 further supports that interfamily marriage and regular milk consumption were consistently linked with much higher risk of attainment of breast cancer; diet showed protective effects against breast cancer in all analyses.

Table 1: Basic information of study subjects

Characteristics	Control (n=1154) n (% within group)	Cases(n=811) n (% within group)	p-value*
Age Groups (Years)			
20 - 30	89 (7.7)	66 (8.1)	0.02
31 – 40	300 (26.0)	209 (25.7)	
41 – 50	474 (41.0)	282 (34.7)	
51 - 60	144(12.5)	101 (12.4)	
> 60	147 (12.7)	154 (19)	
Profession			
House wife	979 (90.9)	767 (94.57)	0.002
Working	98 (9.1)	44 (5.5)	
Married			
Yes	1083 (93.8)	760 (93.6)	--
No	71 (6.2)	51 (6.4)	
Interfamily marriage			
Yes	327 (30.2)	370 (45.6)	<0.001
No	756 (69.8)	441 (54.4)	
Education			
Post-Graduate	70 (6.1)	7 (0.9)	<0.001
Graduate	217 (18.8)	62 (7.6)	
Intermediate	150 (13.0)	69 (8.5)	
Secondary	184 (15.9)	119 (14.7)	
Primary	323 (28.0)	223 (27.5)	
Illiterate	210 (18.2)	331 (40.8)	
BMI			
< 18.5	136 (11.8)	94 (11.6)	--
18.5-25	896 (77.6)	652 (80.3)	
>25	122 (10.6)	66 (8.1)	

p-value* < 0.05 = significant

Table 2: Life style features of study subjects

Characteristics	Control (n=1154) n (% within group)	Cases (n=811) n (% within group)	p-value*
Social history			
Betel nuts	89 (7.7)	75 (9.2)	0.02
Betel leaves	113 (9.8)	49 (6)	
Others (smoking, naswar, gutka)	11 (1.0)	7 (0.9)	
None	941 (81.5)	680 (83.9)	
Regular use of milk			
Yes	346 (30.0)	471 (58)	<0.001
No	808 (70.0)	340 (42)	
Milk type			
Fresh	284 (24.6)	399 (49.19)	<0.001
Pack	62 (5.4)	72 (8.87)	
None	808 (70.0)	340 (41.92)	
Regular use of tea			
Yes	1064 (92.2)	718 (88.4)	0.003
No	90 (7.8)	93 (11.6)	
Diet			
Vegetable	632 (54.8)	441 (54.3)	<0.001
Meat	231 (20.0)	73 (9.1)	
Both	291 (25.2)	297 (36.6)	

p-value* < 0.05 = significant

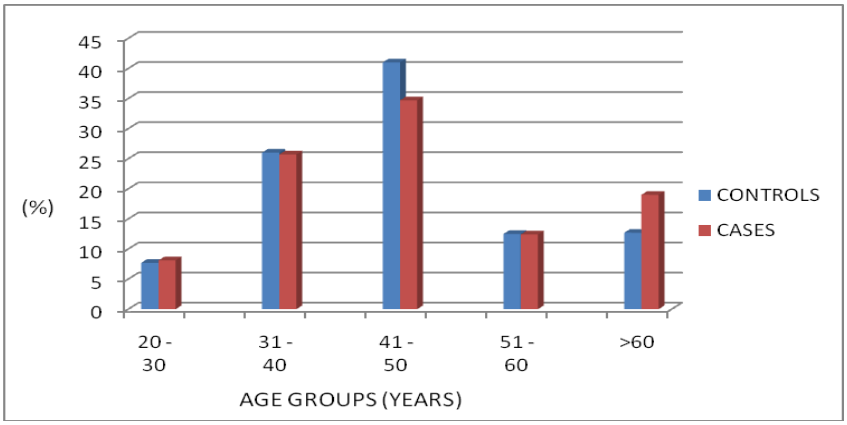

Fig 1: Age distribution among study subjects

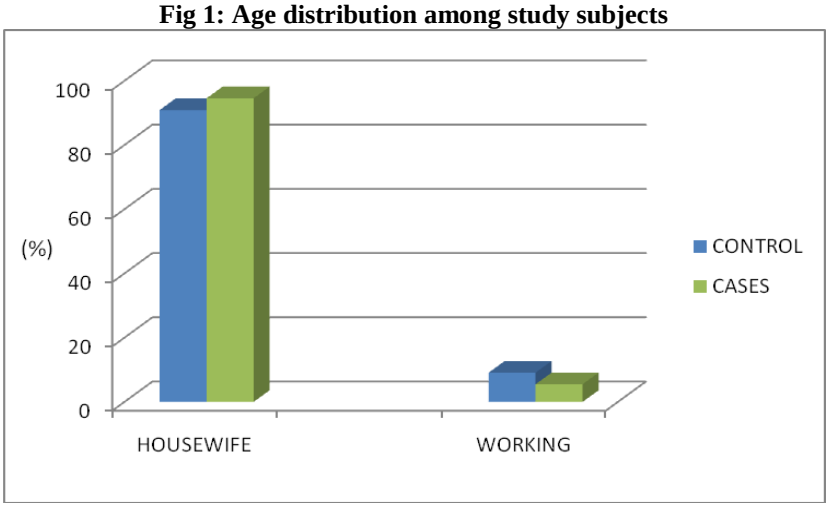

Fig 2: Subjects by profession

Table 3: Disease information of study subjects

Characteristics	Control (n=1154) n (% within group)	Cases (n=811) n (% within group)	p-value*
Family history of breast cancer			<0.001
Yes	0 (0)	127 (15.65)	
No	1154 (100)	684 (84.34)	
Which member has breast cancer			<0.001
None	1154 (100)	684 (84.34)	
Brother	0 (0)	7 (0.9)	
Cousin	0 (0)	14 (1.7)	
Daughter	0 (0)	5 (0.6)	
Son	0 (0)	0 (0)	
Father	0 (0)	11 (1.4)	
Husband	0 (0)	7 (0.9)	
Maternal relative	0 (0)	15 (1.8)	
Mother	0 (0)	14 (1.7)	
Sister	0 (0)	31 (3.8)	
Paternal relative	0 (0)	23 (2.8)	
Concomitant disease in subjects			0.001
No	748 (64.8)	493 (60.8)	
HTN	191 (16.6)	133 (16.4)	
DM	49 (4.2)	35 (4.3)	
HTN+DM	46 (4.0)	69 (8.5)	
Multiple (HTN+DM+Others)	120 (10.4)	81 (10.0)	

p-value* < 0.05 = significant

Table 4: Binary logistic regression analysis for basic features of study subjects

Risk Factors	Frequency (n)	p-value*	Odds Ratio	(95%) C.I
Age Groups (Years)				
20 - 30	155	-----	Reference	-----
31 – 40	509	0.73	0.93	(0.65,1.35)
41 – 50	756	0.21	0.80	(0.56,1.13)
51 – 60	245	0.78	0.94	(0.62,1.42)
More than 60	301	0.08	1.41	(0.95,2.08)
Married -----				
NO	122	-----	Reference	-----
Yes	1843	0.82	0.95	(0.66,1.38)
Profession				
House wife	1740	0.003	1.73	(1.19,2.50)
Working	140	-----	Reference	-----
Interfamily marriage				
No	1197	-----	Reference	-----
Yes	697	<0.001	1.94	(1.60,2.34)
Education level				
Post graduation	77	-----	Reference	-----
Graduation	279	0.13	2.85	(1.25,6.53)
Intermediate	219	<0.001	4.60	(2.01,10.52)
Secondary	303	<0.001	6.46	(2.87,14.54)
Primary	546	<0.001	6.90	(3.11,15.29)
Illiterate	541	<0.001	15.76	(7.11,34.93)
BMI				
18.5-25	1548	-----	Reference	-----
< 18	230	0.72	0.95	(0.71,1.25)
>25	188	0.06	0.74	(0.54,1.02)
Concomitant disease in subjects				
No	1241	-------	Reference	----------
HTN	324	0.66	1.05	(0.82,1.35)
DM	84	0.72	1.08	(0.69,1.69)
HTN+DM	115	<0.001	2.27	(1.54,3.36)
Multiple (HTN+DM+others)	201	0.87	1.02	(0.75,1.38)

p-value* < 0.05 = significant

Table 5: Binary logistic regression analysis for life style features of study subjects

Risk Factors	Frequency (n)	p-value*	Odds Ratio	(95%) C.I
Social history				
No	1622	----	Reference	----
Betel nuts	164	0.35	1.16	(0.84,1.60)
Betel leaves	162	0.04	0.59	(0.42,0.85)
Others (smoking,naswar,gutka)	18	0.79	0.87	(0.33,2.28)
Regular use of milk				
No	1149	----	Reference	--
Yes	817	<0.001	3.22	(2.67,3.89)
Milk type used				
Fresh	683	<0.001	3.49	(2.86,4.26)
Pack	128	<0.001	2.64	(1.82,3.83)
No	1133	----	Reference	----
Regular use of tea				
Yes	1782	0.005	0.64	(0.47,0.87)
No	183	----	Reference	----
Diet				
Vegetables	1073	<0.001	0.68	(0.55,0.83)
Meat	305	<0.001	0.31	(0.23,0.42)
Both	588	----	Reference	----

p-value* < 0.05 = significant

Table 6: Bivariate (adjusted) regression analysis of risk factors of breast malignancy

Characteristics	Adjusted OR (95% C.I)[a]	Adjusted OR (95% C.I)[b]
Profession		
House wife	1.77 (1.20,2.61)	0.94 (0.61,1.47)
Working	Reference	Reference
Married		
Yes	0.90 (0.62,1.32)	0.98 (0.66,1.45)
No	Reference	Reference
Interfamily marriage		
Yes	2.06 (1.69,2.50)	1.82 (1.48,2.23)
No	Reference	Reference
Education		
Post-Graduate	Reference	*(Adjusted)*
Graduate	2.95 (1.27,6.83)	
Intermediate	4.45 (1.94,10.21)	
Secondary	6.73 (2.97,15.26)	
Primary	7.23 (3.24,16.13)	
Illiterate	16.10 (7.21,35.94)	
BMI		
< 18.5	0.96 (0.72,1.27)	1.01 (0.75,1.37)
18.5-25	Reference	Reference
>25	0.74 (0.54,1.02)	0.67 (0.48,0.94)
Concomitant disease in subjects		
No	Reference	Reference
HTN	0.94 (0.71,1.23)	0.75 (0.56,1.00)
DM	1.07 (0.67,1.68)	1.12 (0.69,1.82)
HTN+DM	1.84 (1.20,2.82)	1.56 (0.99,2.45)
Multiple (HTN+DM+Others)	0.92 (0.66,1.27)	0.97 (0.68,1.36)

a- Adjusted for age
b- Adjusted for age and education

Table 7: Bivariate (adjusted) regression analysis of life style risk factors of breast malignancy

Characteristics	Adjusted OR (95% C.I)[a]	Adjusted OR (95% C.I)[b]
Social history		
Betel nuts	1.18 (0.85,1.63)	1.19 (0.85,1.66)
Betel leaves	0.56 (0.39,0.80)	0.60 (0.41,0.87)
Others (smoking, naswar, gutka)	0.88 (0.34,2.31)	0.61 (0.22,1.65)
None	Reference	Reference
Regular use of milk		
Yes	3.17 (2.62,3.83)	3.36 (2.75,4.11)
No	Reference	Reference
Milk type		
Fresh	3.42 (2.80,4.19)	3.64 (2.94,4.51)
Pack	2.65 (1.83,3.85)	2.76 (1.87,4.08)
None	Reference	Reference
Regular use of tea		
Yes	0.61 (0.45,0.83)	0.60 (0.44,0.84)
No	Reference	Reference
Diet		
Vegetable	0.67 (0.54,0.82)	0.65 (0.52,0.80)
Meat	0.28 (0.20,0.38)	0.25 (0.18,0.35)
Both	Reference	Reference

a- Adjusted for age
b- Adjusted for age and education

Table 8: Multivariate adjusted logistic regression analysis for established and suspected risk factors of breast cancer

Characteristics	Adjusted OR (95% C.I)
Age Groups (Years)	
20 - 30	Reference
31 – 40	0.10 (0.04,0.24)
41 – 50	0.06 (0.02,0.14)
51 - 60	0.09 (0.04,0.23)
> 60	0.07 (0.03,0.18)
BMI	
< 18.5	1.32 (0.88,1.97)
18.5-25	Reference
>25	0.91 (0.60,1.39)
Interfamily marriage	
Yes	2.14 (1.64,2.79)
No	Reference
Social history	
No	Reference
Betel nuts	1.10 (0.66,1.85)
Betel leaves	0.45 (0.28,0.70)
Others (smoking,naswar,gutka)	0.30 (0.08,1.05)
Regular use of milk	
No	Reference
Yes	6.02 (4.57,7.92)
Regular use of tea	
Yes	1.01 (0.64,1.59)
No	Reference
Diet	
Vegetables	0.78 (0.59,1.04)
Meat	0.22 (0.14,0.33)
Both	Reference
Profession	
House wife	0.22 (0.11,0.44)
Working	Reference

Adjusted for education

DISCUSSIONS

Breast cancer is the most common cancer of women universally contributing to almost one quarter of all types of female malignancies [2] and has been affecting more than a million females per annum. From Pakistan, studies have revealed breast cancer to be the most common female malignancy [56,57,58].

In this study, the range of age of enrolled subjects was 20-80 years for overall 1154 controls and 811 cases. The controls and cases were frequency matched based on age in this study; therefore, age was regarded as a confounder and included in the regression models for analyses. The mean age of control group was 45.85±9.97 years and that of breast cancer cases was 47.02±11.79 years; this has also been reported in other studies from Pakistan [59,60]. Two largest age blocks of the study subjects comprised of 41-50 years (41% controls and 34.7% cases) and 31-40 years (26% controls and 25.7% cases) respectively (Fig. 1). Few of the subjects were working women by profession in this study and majority was housewives (Fig.2) and married. Consanguineous marriages are common in Pakistan [24] and it was observed in our study that almost 50% of cases had interfamily marriage which is significantly different from that of controls (Table 1).

In this study education has been used as a proxy measure of SES (socio economic status) and this has been done in recent studies also [61]. A considerable difference ($p<0.001$) between the controls and the cases in relation to the distribution of education levels was recognized (Table 1). Majority of our study subjects had a normal BMI (18.5-25 kg/m^2). Table 2 shows the life style features of the study subjects with significant variations among the two groups. Habits like smoking and others were found to be to very less extent in both the groups but eating of betel leaves was somewhat more in the controls (9.8%) as compared to the cases ($p=0.02$). There were 58% cases who were used to drink milk on regular basis as compared to controls (30%) and fresh milk was used up more (49.19%) than milk supplied in packs (8.87%) by the case group ($p<0.001$). The controls were found to be habitual of taking tea more (92.3%) than the cases (88.4%) ($p=0.003$). Regarding the diet, meat intake was found more in the control group (20%) than the case

group (9.1%) who took both vegetarian and meat diet with more frequency (36.6%) than the control group (25.2%) (p<0.001).

From Table 3 it can be seen that only few cases had a family history of breast cancer (15.65%) and none was found in the control group (p<0.001). Concomitant diseases found in the cases and controls were mainly hypertension (16.4% and 16.6% respectively) and multiple diseases (10% and 10.4% respectively) (p=0.001). Diabetes mellitus and hypertension have appeared as chief health concerns worldwide. Approximately 285 million people suffering from diabetes globally were reported in 2010 representing a frequency of 6.4% [47].

A series of logistic regression analyses for various risk factors of breast cancer is illustrated in Tables 4-8. The initial results (Table 4) showed that housewives (p=0.003) and interfamily marriage (p<0.001) were significantly associated with breast cancer risk; the association was consistently shown in the bivariate and multivariate analysis (Tables 6 and 8) revealing that the odds were higher for the risk of attaining breast cancer in the subjects. There are dissimilarities internationally for the occurrence of breast cancer in developed and developing states due to dissimilarities in environmental and genetic aspects. In Pakistan, the probable reasons for high breast cancer incidence in spite of consanguineous matrimonies could be a diminutive account of consanguinity and gene inferences. Yet, consanguinity should be regarded as a possible risk factor for breast carcinoma which may also explain widespread distinctions in breast cancer occurrence [25]. Though house wives by profession were found to have significant higher odds of 1.73 (95% C.I= 1.19, 2.50) in uni-variate analysis (Table 4) in this study which weakened in the adjusted bivariate analysis (Table 6) and became insignificant; it was not further investigated in multivariate adjusted model. It has been stated that women who are not used to physical activities have a predictor of growing breast cancer [62,63].

Regarding the education levels of the subjects of this study, significantly high odds were observed (Table 4) in uni-variate analysis that were consistent in the age adjusted bivariate model for the cases with low education level (Table 6). In contrast, higher level of education in females was found to be linked with further risk of breast cancer in former studies which might be related to dissimilarity in their life style i.e. use of hormonal therapy, use of contraceptives, etc.[64,65] The normal range for body mass index (BMI) is 18.50 to 24.99 kg/m2 [66] and the majority of the subjects enrolled in this study were found having normal BMI. BMI was not established to be associated with breast cancer risk in the univariate analysis (Table 4) though the results exhibited strengthened odds for adjusted bivariate (Table 6) and multivariate (Table 8) models for BMI < 18.5 kg/m^2 but unimportant statistically. This may be due to the inclusion of covariates in these models. Investigations have displayed that higher BMI is related to higher breast cancer threat particularly in post menopausal women and it has been also instituted to hyperinsulinemia and insulin resistance which produces increased risk of developing breast malignancy[67,68].

In this study, hypertension and diabetes mellitus exhibited significant association (OR 2.27; 95% C.I=1.54, 3.36) with breast cancer risk in the uni-variate model (Table 4) but it was inconsistent in the bivariate adjusted models (Table 6). The relationship between diabetes and breast cancer risk has been studied previously [69,70]. Hyperinsulinaemia, has been held as possible cause in attaining breast cancer [48,49]. Furthermore, obesity itself is linked to type 2 DM which elevates endogenous oestrogen levels in the body. Insulin averts the production of sex hormone-binding globulin, ensuing elevated free steroid hormones, specifically free oestrogens [71]. Hyperinsulinaemia may also have joint effects with the insulin growth factor I that could intricate breast cancer-causing developments [50]. It is also reported that chronic hyperglycaemia strengthened breast cancer risk via Warburg effect, in which cancerous cells mainly produce energy by a great level of glycolysis in the cytosol [53, 54]. On the other hand, no drop in the threat of breast malignancy was realized in randomised trials with much more glycaemic control of type 2 DM [72]. Clearly, hypertension without diabetes has been described to increase the risk of breast cancer substantially which might be owing to the genetic mutations in lymphocytes in hypertensive females [73].

Regarding the family history of breast cancer in the enrolled subjects, infinite odds were found in all the binary logistic regression analyses and hence not mentioned in the tables; this has been established through various studies that there is an association between family history and breast cancer risk [74,75,76] which may be due to the relations between genetic and environmental characteristics.

The binary logistic regression results (Table 5) showed that regular consumption of milk (whether fresh or pack) was significantly (p<0.001) related to the risk of breast malignancy (OR 3.22; 95% C.I=2.67, 3.89) which steadily increased significantly in the adjusted bivariate and multivariate models (Tables 7 and 8 respectively). Our findings are consistent with the research in which breast carcinoma has been found linked to dairy products like milk and cheese due to present fats, growth factors like insulin growth factor I and presence of some pesticides (Organo-chlorines) having carcinogenic potential [29]. DDE (a metabolite of DDT) and PCB are the frequently found organo-chlorine remains in human tissues [77]. This is crucial that numerous toxic pesticides and herbicides are being sold in the developing states like Pakistan that are oncogenic, found prevailing not only in the water supplies but also in the air and dust in home environment. Such environmental pollutants are

xenoestrogens which act like estrogens when interacting with breast cancer cell lines [32,33]. Other studies have also established the increase in development of ER+ breast tumors due to DDT [78,79]. Other life style features displayed negative associations with breast cancer risk in all the binary logistic regression models. An opposite association of vegetable and fruit consumption with breast cancer danger but a positive connection of greater meat consumption with breast cancer was reported by Bao et al (2012)[80].

CONCLUSIONS

The risk factors significantly related with breast cancer were found to be education, interfamily marriage, milk consumption particularly fresh milk, family history and diseases like hypertension and diabetes mellitus. Diet was found to be protected through analyses. Inter family marriage and milk consumption were seen to be consistently related with the risk of breast cancer in various analyses. Measures should be taken to ensure prevention from the disease on national level after assessing the risk factors in the local population.

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