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RESEARCH ARTICLE

Evaluation of Common Risk Factors for Breast Carcinoma in Females: a Hospital Based Study in Karachi, Pakistan

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Abstract

Background: Breast malignancies are one of the leading causes of deaths in females worldwide. There are a number of risk factors associated with breast cancer but in Karachi Pakistan there are insufficient data available. **Materials and Methods:** A case control study was conducted on females in age group between 30-80 years. This study was accomplished by retrospective data collection in Aga Khan University Hospital Karachi, Pakistan. A total of 108 females with primary malignancy of breast were included along with 108 matched controls. Relationship of various factors with disease was studied using logistic regression to calculate odds ratios with 95 % confidence intervals. **Results:** A total of 14 variables were analyzed and based on and 7 were found to be risk factors: old age, family history of breast cancer, family history of other carcinomas, personal history of breast carcinoma, early age of menarche, older age of mother at first delivery and lower number of children. Five factors, parity, breast feeding, history of oral contraceptive pills intake, past history of oophorectomy and hysterectomy showed protective associations. One variable, use of hormonal replacement therapy, showed a controversial link and one other, marital status, was not significant in this study. **Conclusions:** It is concluded that most of the well-known risk factors for breast cancer are also associated with the disease in the female population of Karachi, Pakistan. High risk patients should be the focus with the help of this study so that screening can be more effective for early diagnosis before clinically evident breast malignancy.

Keywords: Risk factors - breast cancer - female - mammogram - Karachi, Pakistan

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Introduction

Breast cancer in females is the commonest malignancy globally and it contributes to one third of almost all types of cancers (Kuru et al., 2002). Women mortality triggered by breast carcinoma is the 2nd cause of death in females. (Harrison, 1987). There are a number of etiological factors which can influence breast cancer. There is a paucity of data from Pakistan, especially from Karachi, but these conditions are acknowledged and covered by a number of studies world wide.

There is a wide range of conditions which can influence this disease (Hu et al., 2010): most important factors are old age, family history of breast cancer, early menarche, late menopause, nulliparity, older age at the time of first full term gestation, and hormonal replacement therapy and less number of full term pregnancies. (Nelson et al., 2002; Azizi et al., 2004; Joanna et al., 2014).

Being older is a well-known risk for breast cancer (Narod, 2002). Incidence of breast malignancy is significantly low in younger age group i.e. under the age of 30 years (incidence 25 cases per 10,000) and after the

age of 30 years incidence increases proportionally up to the age of 80 years, after this age there is a decline of disease with incidence of slightly less than 500 cases per 10,000. (Bilimoria et al., 1995; Pirayesh et al., 2014).

The first ever breast cancer was diagnosed over 135 years ago, after which many studies have been conducted. Almost all of those studies were subjected to a meta-analysis by Pharoah et al. in 1997 (Pharoah et al., 1997; Ries et al., 2000) which concluded the association of family history of breast cancer and suggested that this factor is a strong risk for this disease. Another multicenter study which involved 282000 women in 29 different centers reported that in females with early menarche i.e. less than 12 years, risk of breast cancer is higher as compared to the females with late menarche (Fatemeh et al., 2015; Hui et al., 2015).

Late menopause i.e. until 55 years of age is a risk factor as compared to early menopause i.e. before 45 years (Nasim et al., 2014). In the same context, a nulliparous woman and in a woman who had her first full term delivery at or after the age of 30 years, the risk of this disease is higher (Brinton et al., 1988; Kelsey et al., 1990; Goldgar

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National Institutes of Health in 2002 has proven the risk in using HRT (hormonal replacement therapy) over its benefits. The earlier studies also support this fact; according to a study by Nelson et.al there is a 26% increase in the risk of developing breast cancer over a 5 year period of continuous usage of HRT (Nelson et al., 2002; Fathinajafi ., 2003; Nidal et al., 2015).

Unites States of America (USA) Cancer Statistics Working Group revealed incidence count and death count in 2010. The results demonstrated that 206,966 women and 2,039 men in USA were diagnosed with carcinoma of breast and 40,996 women and 439 men in USA died from breast carcinoma.

There is also a rapid abrupt increase noted in the incidence of breast cancer during last few years in Pakistan however a plateau is seen after the age of menopause i.e. after 45 years (Elkum et al., 2014). In Pakistani females breast carcinoma is the most repeatedly diagnosed malignancy; about 1 in every 9 Pakistani females is likely to be affected by breast cancer. This is one of the highest incidence rates in Asia. Incidence rate in Pakistani females is 50/100,000 and our nearby country India the incidence rate is 19/100,000 (U.S. Cancer Statistics Working Group 2013). Due to shortage of tumor registry in Pakistan, epidemiology is difficult and we felt the importance of evaluation of different risk factors among females in Karachi, Pakistan.

Materials and Methods

The presented case control study was conducted on females, age group between 30-80 years. This study was done by a retrospective data collection from a proforma obtained prior to each mammogram in the radiology department, Aga Khan University Hospital Karachi, (AKUH) Pakistan. Ethical research committee (ERC) exemption was acquired from A.K.U.H. E.R.C. committee prior to data collection.

A total of 108 female cases with primary malignancy of breast were acquired and 108 controls were also obtained from same data. Cases were defined as female patients with age range from 30-80 years and with a histopathological proof of breast malignancy. They came for a mammogram in the Radiology Department of Aga Khan University Hospital Karachi, Pakistan. An equal number of controls were selected from same cohort of patient. The controls were healthy and had normal mammogram findings.

All mammograms were performed on Siemens Nova 3000 System and included craniocaudal and mediolateral view of each breast.

Using adequate formulation and considering a confidence interval of 95% and study power of 80%, a total of 216 study subjects including 108 cases and 108 controls were studied. No informed consent was acquired as it was not needed in this retrospective data collection.

Age was matched for both the case and control subjects with an interval of +/- 2 years.

Relationship of variable factors with disease was

studied using logistic regression to calculate Odds ratios (ORs) and 95 % confidence interval (CIs).

Male cases were excluded and exclusion criteria for controls were endocrine disorders, known malignancy, hormonal disease and gynecological diseases.

Results

A total of 108 female cases with primary malignancy of breast were acquired from data of questionnaire used in mammogram and 108 controls were also acquired from same data. Age range was 30-80 years.

Total of 14 variables were analyzed (Table No.1) and based on odds ratio (O.R.) and confidence interval (CI) 7 variables were found to be "*the risk factors*" for development of breast cancer, these factors were; the old age, family history of breast cancer, family history of other carcinomas, personal history of breast carcinoma, early age of menarche, old age of mother at the time of first delivery and less number of children. Five factors i.e. ever pregnant, breast feeding, oral contraceptive pills (OCP) consumption, past history of oophorectomy and hysterectomy showed protective association. One variable i.e. use of HRT (hormonal replacement therapy) showed controversial association and one of the variable i.e. the marital status was not significant in this study.

Mean age of cases and controls was 54.0 years with S.D. (standard deviation) \pm 9.7 and 53.8 years with S.D. \pm 9.3 respectively and range was 30-80 years.

Age group between 41-60 years showed four times risk and age group between 61-70 years showed two times risk to develop breast cancer as compared to the age group between 71-80 years. However the risk was minimal in the age group between 30-40 years.

Having a positive family history of breast cancer (OR 1.8), family history of the other carcinomas (OR 1.3) and personal history of breast carcinoma (OR 7.8) were found to be the risk factors. The latter one showed a significant positive association with breast cancer development.

Among female subjects who had early menarche i.e. at 13 years of age, showed up to five times more risk than those who had delayed menstrual onset i.e. after 15 years of age. Female had menarche at the age of \leq 12 years also showed four times risk as compared to female who had menses after 15 years of age. However female who had menarche at the age of 14 and older did not show significant risk of this disease.

Female subjects who had their 1st full-term delivery at the older age than 22 years showed 15 times risk of this disease as compared to the others who had their 1st full-term delivery at or earlier than 22 years of age.

In this study the risk of having breast cancer was significantly less in females who had more than 3 children compared to those who had 3 (OR 7) or less than 3 live births (OR 2). No significant difference was noted between the subject with live births of 4, 5, 6 or $>$ 6.

Breast feeding (OR 0.025), being ever pregnant (OR 0.018) and consumption of OCP (OR 0.92) showed some protective association with breast carcinoma. Surgical removal of ovaries (OR 0.921) and uterus (OR 0.89) were also found to have slight protective effects.

Table 1. Reproductive and Non Reproductive Representatives of Case and Control Sets Along with OR (CI 95%)

VARIABLE	CASES V/S CONTROLS		
	CASE	CONTROLS	OR(95% CI)
Marital status:			
Married	102 (94.4)	100 (92.6)	1.071 (1.03-1.11)
Single	6 (5.6)	8 (7.4)	1
Age:			
30-40	9 (8.3)	7 (6.5)	1.80 (2.97-1.09)
41-50	34 (31.5)	37 (34.3)	4.32 (1.02-1.82)
51-60	39 (36.1)	37 (34.3)	4.64 (1.10-1.95)
61-70	22 (20.4)	23 (21.3)	2.64 (2.64-2.64)
71-80	4 (3.7)	4 (3.7)	1
Ever pregnant:			
Yes	92 (85.2)	92 (85.2)	0.018 (0.004-0.088)
No	16 (14.8)	16 (14.8)	1
Breast feed:			
Yes	88 (81.5)	90 (83.3)	0.025 (0.005-0.116)
No	20 (18.5)	18 (16.7)	1
Family history of breast cancer:			
Yes	30 (27.8)	10 (9.3)	1.8 (0.548-6.212)
No	78 (72.2)	98 (90.7)	1
History of OCP consumption:			
Yes	10 (9.3)	2 (1.9)	0.921 (0.884-0.959)
No	98 (90.7)	106 (98.1)	1
Family history of other carcinomas:			
Yes	24 (22.2)	16 (14.8)	1.317 (0.354-4.903)
No	84 (77.8)	92 (85.2)	0.947 (0.757-1.185)
Personal history of breast carcinoma:			
Yes	2 (1.9)	2 (1.9)	7.84 (7.84-7.84)
No	106 (98.1)	106 (98.1)	0.98 (0.961-1.0)
History of hormonal replacement therapy:			
Yes	10 (9.3)	0 (0)	0.950 (0.921-0.981)
No	98 (90.7)	108 (100)	1
Age of menarche:			
≤ 12	24 (22.2)	52 (48.1)	4.64 (1.20-1.78)
13	56 (51.9)	40 (37.0)	5.69 (1.54-2.27)
14	22 (20.4)	8 (7.4)	1.03 (0.00-0.00)
≥15	4 (3.7)	8 (7.4)	1
Age of mother at first delivery:			
16 -18	14 (13.0)	16 (14.8)	1.756 (1.756-1.756)
19-22	28 (25.9)	30 (27.8)	1.756 (0.00-0.00)
>22	66 (61.0)	62 (57.4)	15.375 (3.258-72.561)
Number of children:			
0-2	52 (48.1)	40 (37)	2.327 (0.00-0.00)
3	30 (27.8)	16 (14.8)	7.697 (0.00-0.00)
4	8 (7.4)	18 (16.7)	1
6	10 (9.3)	20 (18.5)	1
>6	8 (7.4)	14 (13)	1
History of oophorectomy:			
yes	8 (7.4)	8 (7.4)	0.921 (0.884-0.959)
No	100 (92.6)	100 (92.6)	1
History of hysterectomy:			
Yes	10 (9.3)	12 (11.1)	0.891 (0.84-0.93)
No	98 (90.7)	96 (88.9)	1

History of HRT was found to be controversial factor with slight protective effect in this study.

Marital status did not show any significant association in this study.

Discussion

For precluding breast carcinoma in women, it is

important to see the association of different reproductive and socioeconomic conditions with breast cancer development. Risk factors identification is a vital component in early recognition of breast cancer.

We have found in this study that most of the recognized risk factors were also associated with breast cancer among women representing the Karachi female population and results were also matched with the outcomes of western studies in this respect.

There are many risk factors i.e. the old age, family history of breast cancer, family history of other carcinomas, personal history of breast carcinoma, early age of menarche, older age of mother at the time of first delivery and less number of children; all were related with breast cancer in this population too.

Growing older is one of the major risk factor for breast cancer. In this study mean age of cases and controls was 54.0 years with S.D. \pm 9.7 and 53.8 years with S.D. \pm 9.3 years respectively and the range was 30-80 years. It is also comparable with many of the previous studies. In a study by Afsaneh et al. the mean age of those with breast cancer was 47.63 years and 49.18 years by Zare et al. and 51.3 years by Mosavi et al. (2006) and 48.9 years by Lotfi et al. (Mosavi et al., 2006; M. H. Lotfi et al., 2008; Zare et al., 2013; Afsaneh et al., 2014).

Our study summarized that age group between 41-60 years showed four times risk and age group between 61-70 years showed two times risk to develop breast cancer as compare to the age group between 71-80 years and only slight risk was found in the age group between 30-40 years. Our results were also comparable with the other previously published studies. For the age group between 30-39 years the risk is 1 in 228 (0.44%) but it becomes pronounced for the age under 60 years with risk of 1 in 29; this is reported by Afsaneh et al. (2014).

Eva (S. Eva Singletary., 2003) concluded that if all women less than 65 years of age compared with women aged 65 or older, the relative risk of breast cancer associated with increased age is 5.8.

The chances of having breast cancer become so high if anyone has a relative with breast cancer, like mother, sister, and daughter called 1st degree relatives and cousins, grandmother and aunts called 2nd degree relatives (Ozmen et al., 2009). We have merged the two categories (i.e. 1st and 2nd degree relatives) due to lack of data and compared it with a group of subjects having no relatives with breast cancer. This study showed that positive family history is a risk of having disease and the risk was 2 times higher when family history was positive, which is slightly lower than a study by Lotfi et al. in which the risk was 4 times. The reason of low risk in our study was the limited data. Although a study by Eva, 2003 showed risk of 3.3 times and a study by Elkum et al. reported a risk of 2.18 times, both are comparable with this study (Singletary., 2003; Lotfi et al., 2008; Elkum et al., 2014).

A number of studies have also shown a strong association of family history of breast cancer with this disease (Ali et al., 2015). Family history of other carcinomas also showed mild positive association (OR 1.3) in our study, which matches with the study by Elkum et al. (2014) who also reported mild positive association

with OR 1.01 (Elkum et al., 2014).

If a female had been treated for breast cancer, the risk of developing it again either in ipsilateral breast or metastasize to contralateral breast is higher than a female who never had this disease (Tarek et al., 2009). In this study the risk was 7.8 times which is slightly more than the risk of 6.8 times reported by another study (S. Eva Singletary, 2003), this is most likely due to a fact that our study was not a community based study and the data collection was done by a hospital acquired study.

Breast cells growth is stimulated by the estrogen and prolonged continuous exposure of estrogen can enhance the risk of breast cancer (Zhang et al., 2012). There are certain conditions which are uncontrollable like early menarche and late menopause which causes prolonged exposure of estrogen. In this study female subjects who had early onset of menses i.e. in 13 years showed up to five times more risk than those who had delayed menstrual onset (i.e. after 15 years). Female had menarche at the age of ≤ 12 years showed four times risk as compared to the females who had menses after 15 years of age. This is comparable with another study (Lotfi et al., 2008) who has also concluded that early menarche at 13 years showed 3 times risk and menarche at or earlier than 12 years of age showed 16 times risk. The same is also reported by various authors (Ozkaraman et al., 2015). Similar results achieved by other study (S. Eva Singletary., 2003) which showed that menarche before 12 years of age had a relative risk of 1.3 compare to those who had menarche after 15 years. Similarly late menopause is a risk but in our study we were unable to include this factor due to incompletely filled proforma by the technologist. Reports like Becher et al have concluded a protective role of the late menarche i.e. >15 years of age, against carcinoma breast in female with positive family history of breast cancer (Becher et al., 2003).

Vogel et al has concluded that the risk for breast cancer is related with the increase number of ovulatory cycles that a female undergoes during her lifetime (Vogel et al., 1998). Supported by this theory it has been also observed that a female with her uterus and ovaries removed before the age of 40 years showed a 45% reduction in the risk as compared to female with natural menopause at 50-54 years of age. Our study also concluded removal of ovaries (OR 0.921) and removal of uterus (OR 0.89) as mild protective factors. In the same context, pregnancy reduces the overall numbers of menstrual cycle in women's life so it acts as a protective measure. In our study being ever pregnant was found to be a slightly protective factor (OR 0.018) which is supporting the results by Brinton et al. (1988) who has reported that the risk of having this disease in a nulliparous woman is 1.67 times, another work by White et al. who also valued a relative risk of 1.9 for nulliparous. (Brinton et al., 1988, White et al., 2007).

If a women who had her 1st full-term pregnancy after 30 years of age showed a relative risk of having breast cancer. In this study being older at the time of first delivery was found to be a significant risk factor of breast cancer (OR >15) as well. A study by Brinton et al. (1988) also showed that the risk of breast cancer aggravated in a woman who had her 1st full term pregnancy at or after 30

years of age with a relative risk of 2.23. White et al. also valued a relative risk of 1.9 for those who have giving birth at or after the age of 30 years (Brinton et al., 1988; White et al., 2007). Indian researchers (Pakseresht et al., 2009) showed that the females over 20 years of age at the time of their 1st pregnancy had higher risk with OR 1.63.

Our study concluded breast feeding as a protective measure with OR of 0.025 which matches the values by a meta analysis which concluded breast feeding as a protective factor as pooled OR in 32 studies was 0.89 (Thunyarat et al., 2013). Elkum et al also concluded that the subjects with breast feeding showed a protective effect with OR 0.96 (Elkum et al., 2014).

Prolonged breast feeding i.e. more than 24 months is recommended in the religion of Islam that is the main reason why we have a large number of females in our society with the history of breast feeding.

In this study, only 3 live births and less than 3 live births found to be the risk factor of this disease (OR 7.6 and 2.3 respectively). It is comparable with a study by Lotfi et al. (2008) who has also reported 7 times risk with live births ≤ 3 (Lotfi et al., 2008). Another study by Afsaneh et al. supports our results and considers more number of pregnancies as a protective factor with OR of 2.78 for the 1st pregnancy which declined to OR of 0.72 after 4 full-term pregnancies (Afsaneh et al., 2015).

In our study marital condition was not statistically significant. This is also true in a study by (Lotfi et al., 2008).

In our study, consumption of oral contraceptive pills (OCP) showed a slight protective effect with OR of 0.92, this is comparable with a study by Lotfi et al. (2008) which also showed OR of 0.41, but there a few studies, like by Norsa'adah et al. (2005), lokman et al. (2001), Brinton et al. (1983), Wang et al. (1992) and Kumle et al. (2002) which showed positive association of breast cancer with usage of OCP. (Brinton et al., 1983; Wang et al., 1992; Lokman et al., 2001; Kumle et al., 2002; Norsa'adah et al., 2005; Lotfi et al., 2008).

Use of HRT was found to be a controversial factor as in this study a slightly protective association was noted but in another study (Norsa'adah et al., 2005) no significant association was appreciated. Other studies like a study by Nelson et al. which showed positive association of HRT with breast cancer over a period of 5 years of continuous use but if usage has stopped for more than 5 years then the risk was not significant (Nelson et al., 2002; Alacacioglu et al., 2014). In our study results are controversial, could be due to the fact that there was no data collection about the duration for HRT intake and for how long they have stopped it. Another important thing was the unawareness of patient about the combination of HRT i.e. only estrogen or combination of estrogen and progesterone.

Fortunately alcohol is not openly available in Pakistan and also due to religious restriction its consumption is not a risk factor for this population. Cigarette smoking is also not a common practice in Pakistani Muslim females.

There a few limitations of this study, it was a retrospective, hospital based study and data was limited. A few of risk factors were not documented due lack of entry into the proforma filled by a technologist. Only

those factors were documented which were adequately available. The missing risk factors were: duration of breast feeding, age of menopause, high body mass index, lack physical activity, history of radiation exposure (due to lack of knowledge and lack of literacy), smoking and alcohol consumption.

After completion of this study we felt how essential a large community based study is and we recommend a multicenter study in Karachi to validate the results of this study.

It is concluded that most of the well-known risk factors of breast cancer including the old age, family history of breast cancer, family history of other carcinomas, personal history of breast carcinoma, early age of menarche, old age of mother at first delivery, less number of children; all are also associated with breast cancer in the female population of Karachi Pakistan.

High risk patient can be focused by the help of this study and screening can be more effective in the early diagnosis before clinically evident breast malignancy. The breast cancer screening program would be more preventive and effective if high risk patients are highlighted by the clinician.

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