RESEARCH ARTICLE

Potential Risk Factors for Breast Cancer in Pakistani Women

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Abstract

    <u>Background:</u> **Breast cancer is the most common female malignancy worldwide and its incidence is on the rise in Pakistan. The aim of this case-control study was to quantify the association of various risk factors with breast cancer risk among Pakistani women.** <u>Materials and Methods:</u> **A total of 2,246 women were studied, including 1,238 women with histologically confirmed breast cancer patients and age matched control subjects (N=1008) without breast cancer and other chronic diseases. Subjects were interviewed using a specifically designed questionnaire. Unconditional logistic regression was applied. Subsequent disease-specific mortality was also measured.** <u>Results:</u> **In this study, majority of the breast cancer patients (69.59%) were in age ranges of 40s and 50s. BMI greater than 25kg/m2 (OR=1.57; 95%CI, 1.26-1.90 and OR=1.60; 95%CI, 1.26-2.03), marital status of unmarried (OR=2.03; 95%CI, 1.69-2.44), lack of breast feeding, smoking (current or ever), lack of physical activity and post-menopausal status were found to have significant positive associations with breast cancer. It was also observed that increased parity reduced the disease risk. A larger number of cases (58.1%) had their right breast affected while 22.8% had other complications as well.** <u>Conclusions:</u> **This exploratory analysis indicated a number of risk factors to be associated with increased risk of breast cancer. It was also observed that mean age at diagnosis is a decade earlier than in western countries. It is hoped that our findings will facilitate establishment of adequate evidence-based awareness and preventive measures for Pakistani women.**

Keywords: Breast cancer - case-control study - risk factors - socio-demographic- reproductive - life style - Pakistan

Introduction

    Cancer is one of the most important health problem in many parts of the world (Siegel et al., 2011), a leading cause of mortality in economically developed and second leading in developing countries. Breast cancer accounts for 23% of the total cancer cases (Jemal et al., 2011) and unfortunately its prevalence as a common female malignancy is still rising throughout the world (Althuis et al., 2005).

    Pakistan has the highest rate of breast cancer among Asian countries (Rashid et al., 2006), which accounts for almost 34.6% of all female related cancers (Bhurgri, 2004; Banning et al., 2009). Its frequency in Pakistan is more than two fold higher as compared to the neighboring countries (Butt et al., 2009). The annual age-standardized rate of breast cancer is 69.1 according to the Karachi Cancer Registry, which is comparable to North American and European rates (Bhurgri, 2004). In Asian countries the incidence age for breast cancer is 40-50 years as compared to 60-70 years in the Western countries (Leong et al., 2010).

    Breast cancer is a complex disorder caused by interactions of genetic and environmental factors (Bener et al., 2010). There are multiple factors working together to enhance the probability of developing breast cancer (Hartge, 2003) and also contribute to the variability in incidence of the disease onset (MacMahon, 2006). The menace of breast cancer is influenced by early and late events in life, but the mechanism of differential susceptibility has not been fully explored (Lacey et al., 2009) which complicates the prevention procedures. Some groups are at higher risk including family history of breast cancer, those who give first birth at older ages (Kobayashi et al., 2012), women using exogenous hormones for extended durations (Beaber et al., 2014) and those facing obesity (Bhaskaran et al., 2014).

    Regardless of ethnic and racial origin, all females are at risk of having breast cancer but variations in its incidence among different populations suggest that etiological factors differ in their biologic expression and thus have impact on the disease onset (Penhoet et al., 2005). Population based cancer registries are lacking in

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the developing countries like Pakistan and most of the available figures are centered on data from small units of the population (Valsecchi and Steliarova-Foucher, 2008). It is therefore important to explore the potential risk factors for breast cancer in Pakistani women, which might contribute to current knowledge of this vital topic. The primary aim of this project was to examine the cross-sectional associations of life style, reproductive and socio-demographic risk factors with breast cancer in Pakistani women.

Materials and Methods

Design and data collection

In the present study, we obtained the required information and follow up data from histologically confirmed breast cancer patients on a standardized, structured questionnaire. Information was recorded for different factors including personal, family, disease history and ethnicity of each candidate. This population based case-control study was carried out at the Capital University of Science and Technology previously Mohammad Ali Jinnah University, Islamabad Campus, Pakistan. The study was approved by the Departmental Scientific committee of the University. Data was recorded from breast cancer patients along with comparative controls from NORI (Nuclear Medicine Oncology and Radiology Institute) Islamabad, DHQ (District Head Quarter Hospital) Rawalpindi, IRNUM (Institute of Radiotherapy and Nuclear Medicine) Peshawar and visiting different distant villages in Pakistan. All the participants signed an informed consent document prior to being interviewed. A total of 1238 histologically confirmed breast cancer cases were included in the analysis along with 1008 controls. The vital status of study participants was determined through the hospital records and making personal inquiries to determine whether the participant were alive or dead and to record the date of all deaths.

Data analysis

Efforts were made to frequency match the cases and controls by age, ethnicity and geographical location. We analyzed this data to evaluate the clinic-pathologic features of breast cancer patients in the local Pakistani women. Logistic regression was used to investigate potential associations of different clinical features with breast cancer. Association of variables was measured with ORs and corresponding 95% confidence intervals (CI). Overall survival of the patients after diagnosis was assessed using a Kaplan-Meier curve. All the analysis were carried out with R version x64 3.1.0.

Results

Mean (±standard deviation) age of cases and controls at recruitment was 50.58±10.68 and 54.78±14.52 years respectively. Cases were comparatively younger than the controls. Figure 1 presents the socio-demographic characteristics and potential risk factor for breast cancer patients in Pakistani population. BMI was calculated for all the cases and controls by recording their weight (kg)

and height (m^2). Mean BMI for BC cases and controls were 26.07±4.04 and 25.05±4.25 respectively while range of BMI for both cases and controls was observed as 15.32-35.20 and 17.0-35.40. Among the patients 60.66% were married, 46.53% were nulliparous, 16.88% had 4 or >4 children, 39.98% females breast fed their children. Considering smoking and physical activity, 88.85% were non-smokers and 67.93% were physically active. Post-menopausal women diagnosed with breast cancer accounted for 52.26%.

Table 1 represents the basic clinical features for breast cancer cases. 58.08% were the females diagnosed with right breast affected, 33.20% with left breast and 8.72% with both breast affected. Neoadjuvant therapy is the treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, includes chemotherapy, radiotherapy or hormone therapy. Among the breast cancer cases, 67.37% patients were being under treatment with chemotherapy and 17.45% were patients treated with mastectomy.

Clinicians are well aware of the fact that, all breast cancers do not share the same prognosis and thus require different treatments. Attempts were thus made to characterize and distinguish aggressive and non-aggressive tumors (Singletary and Connolly, 2006). In 1904, the German physician Steinthal (Haagensen, 1971) proposed the division of breast cancer into three prognostic stages: small tumors that appeared to be localized to the breast (Stage I), larger tumors that involved the axillary lymph nodes (Stage II), and tumors that had clearly invaded tissues around the breast (Stage III). In this paper, we followed the above stated classification as, Local,
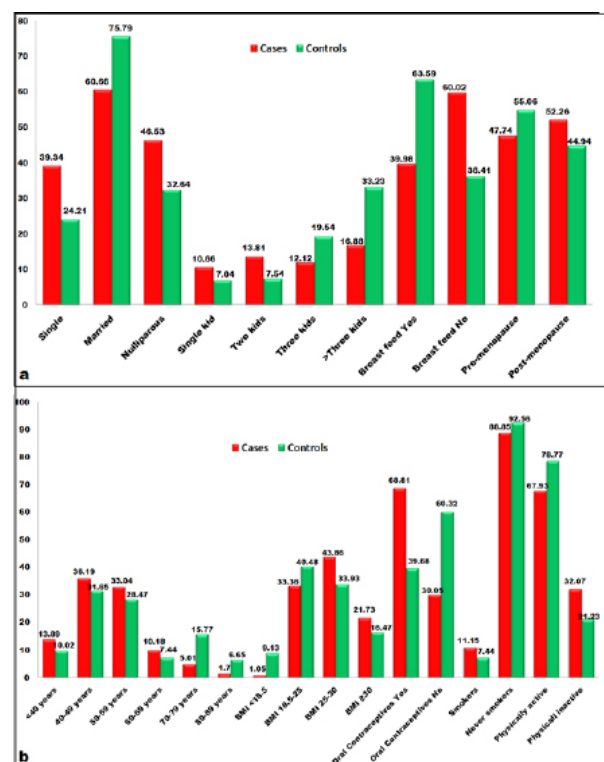
Figure 1. Socio Demographic Characteristics and Potential Risk Factors for Breast Cancer in Pakistani Population. Figures are represented in percentages. a). Reproductive risk factors, b). Life style risk factors

Table 1. Distribution of Breast Cancer Cases by Clinico-Pathologic Features

Patient's pathologic characteristics	Number	Percentage
Breast Affected		
Right Breast	719	58.08
Left Breast	411	33.2
Bilateral	108	8.72
Medical Treatment		
Chemotherapy	834	67.37
Radiotherapy	230	18.58
Both	174	14.05
Surgery Status		
Mastectomy	216	17.45
Lumpectomy	401	32.39
No	621	50.16
Disease Stage		
Local	727	58.72
Locally Advanced	487	39.34
Distant	24	1.94
Other Complications		
Cancer + (any other including Diabetes, Diabetes + HBP, HBP or Others)	282	22.78
No	956	77.22
Family History		
Yes	392	31.66
No	846	68.33
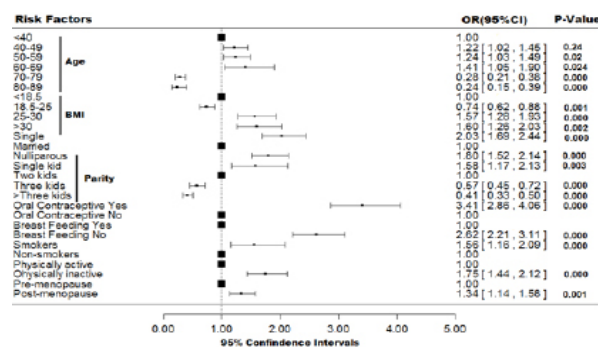
Figure 2. Forest Plot Showing Association of Risk Factors with Breast Cancer in the Study Population.
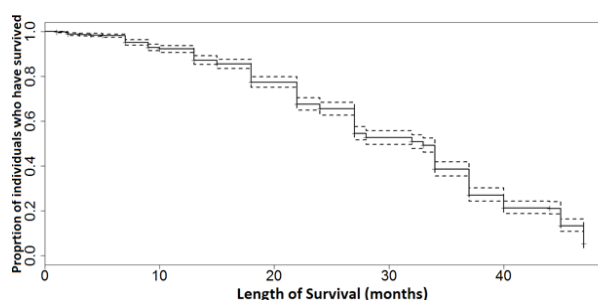
Figure 3. Overall Survival Curve (Kaplan-Meier Plot). Solid line represents survival while dashed lines represent 95% confidence bands

Locally advanced distant metastatic. Disease stage in 58.72% was recorded as local, 39.34% locally advanced and 1.94% were diagnosed with distant metastasis.

Some people are comparatively at higher risk of developing the disease due to various genetic factors. Family history, especially having a close blood relative diagnosed with cancer, doubles the risk of breast cancer. In the current data set, 31.66% patients had at least a blood relative diagnosed with some type of cancer, mostly breast cancer. It was also observed that 22.70% patients were diagnosed with other types of medical conditions including high blood pressure, diabetes etc. as well.

Our results revealed significant association between different factors recorded for breast cancer patients. There was a significant association between age and breast cancer. Females having ages from 40 to 69 years, patients aged in 40s (OR=1.22, 95% CI: 1.03-1.46), 50s (OR=1.24, 95% CI: 1.03-1.49) and patients aged 60s (OR=1.41, 95% CI: 1.05-1.90) were more likely to have breast cancer.

Obesity has a vital role in breast cancer growth and development (Amadou et al., 2013). To examine the influence of this significant risk factor on Pakistani women with breast cancer, we examined this link among breast cancer cases and controls. An increase in the basic metabolic index is positively correlated with breast cancer and thus the proportion of females having BMI≥25 was significantly higher among the patients. Overweight (BMI≥25) and obese (BMI≥30) females have approximately 1.5 times more risk of having breast cancer (Overweight; OR=1.52, 95% CI: 1.28-1.81 and Obese; OR=1.41, 95% CI: 1.14-1.74). So undoubtedly, obesity is a major risk factor for breast cancer among Pakistani women.

It was also observed that unmarried women were at more than two fold higher risk (OR=2.03, 95% CI: 1.69-2.44). Nulliparous women had higher risk for breast cancer (OR=2.56, 95% CI: 1.87-3.51) compared to parous women. It was further observed that the risk decreases with increase in parity. Among the parous women never breastfeeding females were have more than 1.5 fold higher risk of developing breast cancer (OR=1.82, 95% CI: 1.35-2.46). Similarly use of oral contraceptives (OR=3.41, 95% CI: 2.86-4.06), and smoking (OR=1.56, 95% CI: 1.16-2.09) were also significantly associated with increasing risk of breast cancer. Individuals who were physically inactive were recorded to be 1.27 times more likely to develop breast cancer than those who are physically active (OR=1.75, 95% CI: 1.44-2.12). When the menopausal status was studied, we have found approximately 1.34 fold increase in the disease risk among the postmenopausal patients (OR =1.34, 95% CI: 1.14-1.58) (Figure 1). A total of 269 patients were censored during the study out of the total 1238. The patients had an overall median survival time of 33 months (95% CI: 28-34) (Figure 2).

Discussion

Breast cancer is the most frequently diagnosed cancer in Pakistani females (Bhurgri, 2004). The Pakistani population has a large increase in its incidence among Asian countries (Liede et al., 2002). This ongoing trend in rise of breast cancer cases has created an urgent need to develop preventive strategies (Bouguerra et al., 2014). Age is an important risk factor for different cancers (White et al., 2014). Higher proportion of patients has been diagnosed with breast cancer by the age of <40, 40s and 50s year of ages. Mean age at the time of diagnosis

of breast cancer in the present study was observed to be 51.40±10.40, ranging from 29-87. Almost similar pattern of age at diagnosis has been reported by other researchers (Siddiqui et al., 2000; Bhurgri, 2004). A study conducted on Iranian women reported that patients were mostly aged above 44 (Bidgoli et al., 2010). The average age breast cancer incidence among white females in the United States is 61 years (Jatoi and Anderson, 2010), while it is 51.4 years in Pakistani females according to our study. It is almost a decade earlier, as compared to other parts of the world specially the Western countries. The reason for this early age incidence among Pakistani women needs to be further investigated.

Obesity is a common health problem and its frequency is globally increasing. It is well established that increased BMI is related to enhanced incidence of certain diseases including cancers and is also associated to higher morbidity (Must et al., 1999). Patients having a normal BMI have a comparatively longer overall survival rates as compared to the overweight or obese patients (Berclaz et al., 2004). In the current report the mean BMI was observed to be 22.64±3.19 ranging from 15.32-35.20. This case-control study found that, the risk of having breast cancer elevates with increased BMI. Only 33.36% of the study subjects were having BMI in the normal range (18.5-23). The risk of carcinoma increased as the BMI increased from the normal range. Other studies also found that females with high BMI were at increased risk of breast cancer (Ozmen et al., 2009; Bhaskaran et al., 2014; Xia et al., 2014), which may be mainly due to higher levels of free estrogen produced by excess aromatase activity in the peripheral adipose tissue (Bulun et al., 2012).

Tobacco use and physical inactivity are the leading causes of the major non-communicable diseases, including certain types of cancer. Both of these factors are though preventable but contribute significantly to the global burden of disease, death and disability (Organization, 2002). These factors are modifiable and can be prevented (Rose et al., 2008). It is now evident that overweight/ obesity and physical inactivity are major risk factors for developing breast cancer in many countries (Bray et al., 2004). More commonly, people in the urban areas are physically inactive and appropriate measures are therefore needed to avoid weight gain, which would be cost effective than the treatment and allied obstacles. Tobacco smoking is among the leading preventable risk factors for cancer in general (Vainio et al., 2001) and its relationship with breast cancer risk is also uncertain.

There exists a positive association between being physically inactivity and breast cancer risk in Pakistani women (OR=1.72, 95% CI: 1.44-2.12). The relationship between breast cancer risk and physical activity is complex and therefore need to be described through molecular mechanisms from different angles. Physical activity has a multi-dimensional impact on breast cancer because it also other associated risk factors including BMI, menstrual cycle, hormones and immune system (Bernstein et al., 2005). It is now well established that physical inactivity results in an increase in obesity, which has independently been considered a risk factor for breast cancer. There exists an inverse correlation between physical activity

and obesity (Sheppard et al., 2011).

Research has showed that marital status somehow affect an individual's health but this association has not been studied comprehensively (Osborne et al., 2005; Floud et al., 2014). Married women were less likely to have breast cancer according to our results (OR=0.49). Some other researchers have also reported an association between marital status and multiple cancers, which support our results that unmarried individuals are at greater risk in the population. Aizer and colleagues found that unmarried individuals have significantly higher risk of metastatic cancer (Aizer et al., 2013).

In general, reproductive factors, like parity and breastfeeding have already been revealed to have a protective significance against breast cancer (Bernstein, 2002). Parous females have a comparatively lower risk, but this relationship is very complex (Kelsey et al., 1993). In our study we observed that, breast cancer risk gets decreases with increasing parity. Higher the number of full-term pregnancies, the greater the protection. It was observed in the results that cases were less likely to have breastfeed (OR=0.55). These findings are consistent with the findings of some other studies (Hadjisavvas et al., 2010; Kotsopoulos et al., 2012; Babita et al., 2014; Elkum et al., 2014) but further research is recommended to explore the causal mechanisms that how breastfeeding influence breast cancer. Both Pregnancy and breastfeeding reduces the lifetime number of menstrual cycles of a woman and thus her total exposure to endogenous hormones. In addition, breastfeeding and pregnancy also has direct effects on breast cells differentiation and maturation. Differentiated cells are comparatively more resistant to be transformed into cancerous cells (Russo et al., 2005; Britt et al., 2007).

Usage of oral contraceptives has modernized the reproductive life of women (Barrett-Connor, 2002) but only few studies have been carried to investigate the possible association between oral contraceptives and breast cancer. The reported studies have suggested little or no link for this association (Marchbanks et al., 2012). We recorded in our study a positive association between breast cancer risk and usage of oral contraceptives. Our results are in line with other studies, who also have reported that women having used oral contraceptives are at comparatively higher risk of having breast cancer (Dumeaux et al., 2003; Silvera et al., 2005). The hormonal effect posed by the oral contraceptives is complex. They may cause protective anovulation on one hand or may also can stimulate mitotic activity through the mixture of estrogen and progesterone in breast tissues (Pike et al., 1983). Experimental data also support the fact that, estrogens are associated with the growth and development of breast cancer and exert both direct and indirect proliferative effects on human breast-cancer cells (Lupulescu, 1995).

Menopause is not directly related to cancer, but actually the risk of developing cancer increases with the increasing age (Surakasula et al., 2014). During the reproductive age of females, the ovaries produce steroid hormones affecting function and development of the breast (Cancer, 2012).

In conclusion, The current data support that various risk factors including age, BMI, marital status, parity, oral contraceptives, breast-feeding, smoking, physical activity and menopausal status were significantly associated with increased risk of developing breast cancer in Pakistani women. The role of breastfeeding, ages at menarche and menopause needs clarification and further work. It would be useful to confirm these findings in additional studies that include area-based data to capture the ethnic differences in breast cancer cases.

Acknowledgements

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Newly diagnosed without treatment