RESEARCH COMMUNICATION

Increased Risk of Breast Cancer in Multiparous and Lactating Women Attending A Breast Care Clinic in Pakistan: A Paradigm Shift?

Nosheen Fatima, Maseeh uz Zaman*, Tehseen Fatima

Abstract

Aims and Objectives: A changing paradigm shift with multiparity (MP) and breast feeding (BF) has been reported in recent years in breast cancer (BC). Our aim was to observe associations of parity, BF and other risk factors with BC among a local population attending a breast care clinic. Materials and methods: A total of 1,039 women (mean age 39 ± 15 years) attended for screening or presented with palpable breast lumps at KIRAN, Pakistan. The majority were in middle and low socioeconomic strata. As per American Cancer Society (ACS) guidelines 2003, mammography and ultrasound were performed, along with fine needle aspiration cytology (FNAC) in 195 women with Breast Imaging Reporting and Data Set (BIRADS) IV/V, high risk patients with BIRADS III on mammography and with suspicious ultrasound findings. Results: The study population was stratified into two groups; one with BC on FNAC in 181 women (17% p<0.001) and other including 858 healthy women after screening for cancer. The BC group had relative predominance of MP (86% p<0.001), BF (85% p<0.001), family history FH (8% p=0.106) and post-menopause PM (49% p<0.001) as compared to the healthy population. Estimated relative risk (RR) of BC in women with MP, BF, F/H and PM was 3.12 (95% CI=2.05-4.73; p <0.001), 2.47 (95%CI=1.69-3.61; p<0.001), 1.45 (95%CI=0.93-2.41; p=1.06) and 2.33 (95%CI=1.70-3.02; p<0.001) respectively. Higher incidence of BC was observed between 30-40 years 23% (p<0.001) and between 40-50 years 38% (p<0.001). Conclusion: MP, BF and PM have significant associations with BC in the studied Pakistani women and this possible paradigm shift now needs to be evaluated for confounding factors.

Keywords: Breast cancer - multiparity - breast feeding - menopause - Pakistani women

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Introduction

Breast cancer is the most commonly diagnosed cancer in women world wide (Parkin and Whelan, 2000). A rapid rise in annual incidence rate of breast cancer has been observed between 1975-1990 in Asian and African than North American and European women (Sasco, 2001). The published data from Karachi Cancer Registry, the reported incidence of breast cancer was 34.6% and observed as the most common cancer among Pakistani women compared to other Asian countries (Bhurgri, 2004).

High rates of breast cancer in developed countries are associated with increase prevalence of known risk factor like early menarche, nulliparity or low parity, late age at first or any birth and late menopause (Pike et al., 1983). The higher parity, earlier age at first pregnancy and breast feeding for longer duration might account for relatively lower incidence of breast cancer in developing countries (Lane-Claypon, 1926; Beral, 2003). However the recent data show a higher proportion of early onset breast cancer in developing countries as compared to the developed world (Parkin and Whelan, 2000). Furthermore data show multiparity and shorter duration of breast feeding might increase the risk of more aggressive breast cancer (Shinde et al., 2010). This fact is unexpected, as multiparity, early first full term pregnancy and breast feeding are much more common in developing world than in developed countries (Bageman et a l., 2007). Various studies have indicated important role of genetic factors resulting in early onset breast cancer in multiparous African-American women than white women in USA (Amend et al., 2006; Ries et al., 2006).

With this paradigm shift governed by genetic factors, the aim of this study was to observe any association between parity, breast feeding and other risk factors with breast cancer among a local population attending a breast care clinic.

Materials and Methods

This is a prospective comparative analysis included all women attended breast care clinic at Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan from March 2006 till December 2009. Total 1,039

*Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi Pakistan. *For correspondence: masseh.uzzaman@aku.edu*

women attended for screening or presented with history of palpable breast lump. Majority of women were belonged to middle and low socioeconomic strata. Detailed history including information about menarche, menstrual history, menopause, parity, lactation, family history for breast cancer in first degree relative and use of oral contraceptive or hormone replacement therapy (HRT) were taken. Those women with 2 or more than 2 children were considered as multiparous and 1 child or never had a child labeled as low parity or nulliparous respectively. The breast feeding was defined as lactation for more than 2 months. Women who had not experienced a menstrual period during the last year were defined as postmenopausal. Patient who had recently been diagnosed and treated for another type of cancer were excluded from this study. As per American Cancer Society (ACS) guidelines 2003 (Smith et al., 2003), mammogram and ultrasound breast were performed in those women. All women more than 40 years or selected cases of less than 40 years (suspicious lump or strong family history) were subjected for mammography while ultrasound performed in younger women less than 40 years. All patients with BIRADS IV and V, selected high risk patient with BIRADS III on mammography and with suspicious findings on ultrasound were subjected to FNAC.

Statistical Analysis

Data was analyzed by using the MedCalc statistical software version 11.3.10 and SPSS software version 10. For univariate analysis Chi square test was performed for dichotomous variables with Yates correction for continuity and Student's t-test was used for continuous variables. Relative risks with 95% confidence intervals (CIs) were calculated. For all P-values <0.001 were selected as significant.

Results

Total 1039 women with mean age of 39±15 years were registered in breast care clinic. Five hundred women (48%) presented with clinical history of lump on breast self examination (BSE) while remaining 539 (52%) women attended for screening purpose without clinical palpable lump. Mammography was performed on 525 (51%) women and they were classified as BIRADS I in 218 (42%), BIRADS II in108 (20%), BIRADS III in 37 (7%), BIRADS IV in 122 (23%) and as BIRADS V in 40 (8%). Remaining 514 (49%) women were subjected for breast ultrasound, among them 395 (77%) ultrasound was absolutely normal, 92 (18%) was benign pathology and

Table 1. Demographic Distribution of the Study Population

	Total population (n=1039)	BC (n=181)	No BC (n=858)	P value
Age (mean ±SD) years	39 ± 15	40 ± 13	37 ± 14	<0.001
MP (≥2)	712 (68%)	156 (86%)	556 (65%)	<0.001
(mean para ±SD, mean IPI±SD)	(3 ± 2, 24±6 months)	(4 ± 2, 20±5 months)	(3 ± 2, 22±6 months)	
LP (<2 or NP)	327 (31%)	25 (14%)	302 (35%)	
BF (>2 months	715 (69%)	153 (85%)	562 (66%)	<0.001
(mean duration ±SD)	(12 ± 3 months)	(13 ± 2 months)	(12±3 months)	
BF-(<2 months)	324 (31%)	28 (15%)	296 (34%)	
FH +	55 (5%)	14 (8%)	41 (5%)	0.106
FH –	984 (95%)	167 (92%)	817 (95%)	
PM	300 (29%)	88 (49%)	212 (25%)	<0.001
(mean age ±SD)	(47 ± 3 years)	(46 ± 2 years)	(47±3 years)	
Pre-M	739 (71%)	93 (51%)	646 (75%)	

SD, standard deviation; MP, multiparity; IPI, inter pregnancy interval; LP, low parity; NP, nulliparity; BF, breast feeding; FH, family history; PM, post menopause

Table 2. Estimated Relative Risk in Study Population

Risk Factor	BC Present (n=181)	BC Absent (n=858)	Relative Risk (95%CI)	χ^2 value	p-value
MP (≥2)	156	556	3.12 (2.05-4.73)	34.78	<0.001
LP (<2& NP)	25	302			
BF + (>2 months)	153	562	2.47 (1.69-3.61)	25.04	<0.001
BF – (< 2 months)	28	296			
FH +	14	41	1.45 (0.93-2.41)	2.61	0.106
FH -	167	817			
PM	88	212	2.33 (1.79-3.02)	41.61	<0.001
Pre-M	93	646			
MP (≥2)+BF	151/683	532/683	3.54 (0.93-6.47)	22.85*	<0.001
LP (<2&NP)+BF	2/ 32	30/32			
MP (≥2)+FH	11/40	29/40	1.34 (0.83-2.28)	1.62*	0.203
LP (<2&NP)+FH	3/15	12/15			
LP (<2&NP)+FH	3/15	12/15	2.84 (1.74-4.62)	16.99*	<0.001
LP (<2&NP)-FH	22/312	290/312			

CI, Confidence Interval; MP, multiparity; LP, low parity; NP, nulliparity; BF, breast feeding; FH, family history; PM, post menopause; Pre-M, pre-menopause; *Yates correction for continuity

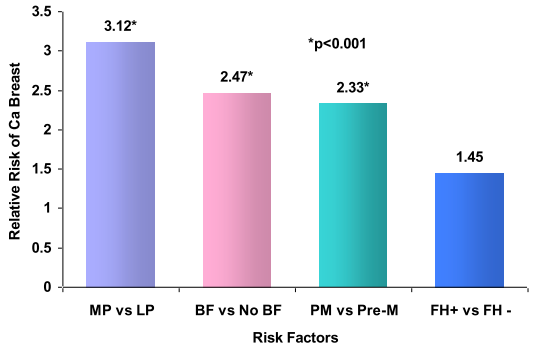

Figure 1. Histogram of Estimated Relative Risk of BC in Study Population. MP, multiparity (>2); LP, low parity <2 or nulliparity); BF, breast feeding; FH, family history; PM, post menopause; Pre-M, pre-menopause

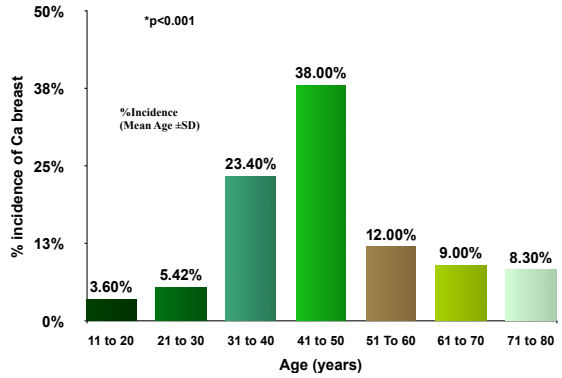

Figure 2. Age-wise Distribution of Incidence of BC in Study Population

27 (5%) ultrasound was suspicious findings. FNAC was performed in 195 (19%) women and 181 (17% p <0.001) were diagnosed as breast cancer.

Study population was stratified into two groups; one with breast cancer included 181 women and another group included 858 healthy women after screening. Breast cancer group had relative predominance of multiparity (86% p<0.001), breast feeding (85% p<0.001), family history (8% p=0.106) and post-menopause (49% p<0.001) as compared to healthy population (Table 1).

Estimated relative risk (RR) of breast cancer (Table 2) in multiparous (mean para ± SD 3±2) versus low parity or nulliparous women was 3.12 (95% CI=2.05-4.73; p <0.001), in history of breast feeding versus without breast feeding was 2.47 (95%CI=1.69-3.61; p<0.001), in positive family history versus no family history of breast cancer was 1.45 (95%CI=0.93-2.41; p=1.06) and in post-menopause (mean age±SD 46±3) versus pre-menopause women was 2.33 (95%CI=1.70-3.02; p<0.001). Figure 1 demonstrated the significant causal relationship of multiparity, breast feeding and menopause with breast cancer, positive family history of breast cancer in our population contributed as non significant relationship with breast cancer neither as a risk factor nor confounding factor (p=0.203) with multiparity, however it was significant when family history present among low parity or nulliparous breast cancer patients with RR of 2.84 (95%CI=1.74-4.62; p<0.001, Table 2). Breast feeding was considered as a significant risk factor for breast cancer alone as well as confounding factor with multiparity (RR=3.54; 95% CI=0.93-6.47; p<0.001, Table 2).

When further stratified into age wise classes (Figure 2), the incidence of breast cancer was significantly observed between 30-40 years 23% (p<0.001) and between 40-50 years 38% (p<0.001).

Discussion

The incidence of breast cancer in Pakistani women is highest as compared to other Asian countries (Bhurgri, 2004). The incidence of breast cancer at breast care clinic of this tertiary care hospital is 17% over a 3 years screening period. The peak incidence of breast cancer in studied population was found between 30-50 years. This is relatively at younger age as compared with western and developed countries (Bageman et al., 2007). Epidemiological studies have shown that incidence of early onset breast cancer is more common in African-American women as compared to white American women (Amend et al., 2006). This draws our attention to a possible role of genetic factor associated with early onset breast cancer in black and possibly Pakistani women as well. Higher level of circulating insulin-like growth factor (IGF-1) is a known risk factor for early onset-breast cancer (Peyrat et al., 1993; Hankinson et al., 1998; Fletcher et al., 2005). Various studies have shown presence of IGF1-19/-19 genotype in black women than white and importantly in 16% of Indian-Pakistani and 33% of other Asian women (Jernstro et al., 2010; Wen et al., 2005). Various studies have also shown that early onset breast cancer is associated with increased incidence of aggressive breast cancer in carrier of BRCA1 germ line mutation and among premenopausal black women (Carey et al., 2006; Millikan et al., 2008; Reis and Tutt, 2008; Schneider et al., 2008). However, we certainly lack this information in studied population which is a limitation of this study indeed.

Reproductive risk factors like multiparity, breast feeding and early menopause are generally considered as protective for breast cancer (Lane-Claypon, 1926; Beral, 2003). But our data show increased incidence of breast cancer in multiparous female as compared with low or nulliparous women. This finding is deviated from the established fact that multiparity is a protective factor against breast cancer. We really don't have a valid explanation for this observed fact but presume that some genetic alone or in combination with other non-genetic factors might have played an important role in our multiparous women. Bageman et al., 2007 reported a significant association of multiparity with IGF-19/19 genotype with early onset breast cancer. Important to note the circulating level IGF-19/19 is three times more common in black women and 16% of Indian-Pakistani women (Wen et al., 2005; Jernstro et al., 2010). Various epidemiological studies have shown that pregnancy has a dual effect on risk of breast cancer; it transiently increases the risk after child birth (short term effect) by stimulating the growth of cells that have undergone the early stages of malignant transformation but reduces the risk in later years (long term effect) by inducing the differentiation of normal mammary stem cells that have the potential for neoplastic changes (Lambe et al,. 1994). Although we

dont have scientific evidence in our women, but we may hypothesize that raised level of IGF-1 with detrimental short term effect of pregnancy might have played a pivotal role in our multiparous women.

Breast feeding in this study showed a significant association with breast cancer and importantly plays a confounding role with multiparity than in low or nulliparity. This is again contradictory to the general understanding of protective role of lactation against breast cancer. Studies have shows that with longer duration of breast feeding the progenitor cells in lactating ducts go into natural differentiation and apoptosis (Russo and Russo, 1994; Symmans et al., 2005; Howard and Ashworth 2006). However, in a recent unpublished report from Switzerland by Salma Butt, longer duration of breast feeding has been found to be associated with more aggressive breast cancers (Butt S, 2010). In our studied women, mean duration of breast feeding was 12±3 months which is adequate but shorter than Muslim norms (18 months as per basic Islamic teaching) and the basic reason is repeated pregnancies at shorter durations. The inter-pregnancy interval (IPI) in women with BC was 20±05 months as usually Pakistani women in low or medium socioeconomic strata do complete their families in 10 years time.

It is presumed that multiparity and short duration of breast feeding results in failure of progenitor cells to undergo natural differentiation and result in increased pool of cells with survival capability and potential risk of carcinogenesis. This is an indirect support of an association of multiparity and breast feeding as pathogenesis has not been tested at a biological level.

Furthermore, level of circulating prolatcin increases during pregnancy because of production from non-pituitary sources like breast, endometrium and T cells (Montgomery et al,. 1990; Gellersen et al., 1994; Clevenger et al., 1995). Several studies demonstrated that prolatcin mRNA is produced in normal human breast tissue (Fields et al,. 1993; Reynolds et al,. 1997) and that breast cancer cells can synthesize appreciable quantities of prolactin in vitro (Clevenger et al., 1995; Ginsburg and Wonderhaar 1995; Reynolds et al,. 1997; Wennbo et al,. 1997). In-vitro studies have also shown that prolactin enhances the response of breast tissue to estrogen by over-expression of estrogen receptors and inhibits apoptosis of breast cancer cells lines (Brockman et al,. 2002; Clevenger et al., 2003; Gutzman et al,. 2004). So these facts might be responsible for sustained stimulation of breast tissues from prolactin and estrogen due to repeated pregnancies at shorter intervals and lactation.

Furthermore, mean age of menopause in our studied population is 46±3 years as compared to mean 51 years in western women (Soules, 2001). The peak incidence of breast cancer in our studied women was found in perimenopausal and early menaopause phases of their reproductive life. This is contradictory to the well known observation that late menopause increases the risk of breast cancer. In western women, median age of breast cancer is 60 years and only 4% of women are 40 years or younger (Bageman, 2007). The plausible explanation in our women could be the nullifying effect of prolonged and sustained exposure of breasts to estrogen and prolactin due to repeated short interval pregnancies against early relatively early menopause.

Family history did not show a significant association in multiparous women as compared to low parity cohort (p-value <0.001). We don't have a valid justification for this association due to lack of fundamental facts in this regard.

Therefore, this study upon Pakistani women attending a breast care clinic shows a paradigm shift in breast cancer risk factors as it was more prevalent in multiparous, lactating women with a relatively early onset as compared with women of developed world. Although we don't have scientific evidence but hypothesize that various genetic factors (like raised level of IGF-1) and non-genetic factors (like prolong and sustained stimulation of breast by estrogen and prolactin resulting from repeated pregnancies at short interval) might play an important role in Pakistani women. This demands a large and multicentre trial with emphasis on exploring the causal relation of various genetic and non-genetic factors possibly involved in breast cancer in our women.

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