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Clinical Research

Status of Familial and Non-Familial Cancer Cases among the Breast Cancer Population in Chennai, Tamil Nadu, India.

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ABSTRACT

Background: A number of studies have investigated familial breast cancer in India, however, these studies have only been done in few states across India. Due to cultural and socioeconomic differences, particularly intra-caste marriage that varies among Indian states as well as environmental, nutritional, and lifestyle factors, it is imperative to assess the impact of familial breast cancer incidences in each and every state in the country. Our study investigated the familial breast cancer cases in Chennai, Tamil Nadu, India where there are a large number of intra-caste marriages.

Materials and Method: 512 breast cancer cases and 540 age matched controls were selected from various hospitals of Chennai. Women, of all ages, were given a questionnaire that evaluated, familial cancer, age of diagnosis, stages of cancer, laterality of breast cancer, types of treatment, and psychological counseling. These results were then analyzed using Karl Pearson statistical test.

Results: In Tami Nadu, only a fraction, 13%,of breast cancer patients had familial breast cancer history compared to the 87% with non-familial breast cancer. The occurrence of breast cancer cases in age groups, 41-45, 46-50 and 51-60 years are significantly higher than other age groups (χ^2: 60.6719, P=<0.001). Notably, we observed an age shift in breast cancer cases from 45-50 to 35-45 years, indicating that an increased number of women in younger age brackets are being afflicted with the disease. Breast cancer stages I and II were significantly higher than stages III and IV ($p<0.001$). Further, incidences of breast cancer on the left side were more prevalent than on the right side of the breast with significantly higher positive axillary lymph node at the time of diagnosis.

Conclusion: The study revealed that there is a very low familial breast cancer incidence in Chennai, including a shift in cancer rates to women of a younger age, implying that the risk factors such as environmental, dietary habits, and lifestyle may possibly be involved in the genesis of breast cancer rather than genetic factors. Thus, lifestyle modifications and educating the population of risk factors may be better avenues for future studies to pursue in order to reduce the risk of breast cancer.

KEYWORDS : Familial breast cancer – TNM stages – Axillary Lymph node – Age shift -Dietary habits– Lifestyle.

Introduction:

Breast cancer is the most common cancer in women worldwide with a widely variable incidence rate between countries and regions. In developed countries, which accounts for a small proportion of the world population, about 50% of breast cancers are diagnosed (1,2). The lowest breast cancer incidences were reported in far Eastern and South East Asian countries (3,4). However, the burden of health care costs on the account of breast cancer has been steadily increasing in the developing countries of Asia. In the coming decades, developing countries will account for a majority of new breast cancer patients diagnosed on a global level. Further, more than 100,000 new breast cancer cases are expected to be diagnosed annually in India (4,5).

In South India, inbreeding such as uncle-niece marriage, or cousin-cousin marriage, a male marrying his maternal uncle's daughter, has been traditionally followed since immemorial time (6), adding to the concern that familial breast cancer could be rampant in this region. A family history of breast cancer in the mother, father, sister, or daughter increases the risk of breast cancer and the risk is increased if the family member diagnosed before the age of 50 years old and/or with premenopausal breast cancer (7,8). Only 5-10% of breast cancers has hereditary origins (9). In addition, a number of other studies have indicated that there is a low rate of BRCA mutations in most populations with only 6-10% of patients with breast cancer screening positive for the mutation in BRCA gene, irrespective of their family history (2). Puri et al. (10) reported that in Chandigarh, India only 3% breast cancer cases had family history, while 97% did not. In New Delhi it was reported 96.6 % of breast cancer cases and 99.1 % controls did not have breast cancer in the family (11). A similar observation was reported in Karnataka (12) and in Tirupati (13). In North Karnataka, Kulkarni et al. (14) reported only 7.19% of breast cancer patients had breast cancer history and the remaining did not. In Punjab, Chopra et al. (15) reported that only 2% of breast cancer cases were correlated with family history of cancer. About 5% of all patients had a family history of breast cancer albeit higher rates of breast cancer among Christians and Parsis compared to Hindus and Muslims (16,17). Studies have shown that there is a lower incidence of family history in breast cancer patients, with only 11% of breast cancer patients having a first degree relative compared to the 5% of patients in the control group, and less than 1% patients have both a mother and sister with disease (18,19). While 5-10% of all cancer cases are due to genetic defects, 90-95% of cases are due to environment and lifestyle, which provides major opportunities for programs that prevent cancer (20). Further, when comparing the stages of presentation of breast cancer, stage 0 and stage I were reported in Western countries in women aged 60-70 years (21), whereas in India the majority of new cases were found in advanced stages (stage III or IV) of the disease (22) and presented in Indian women of 40–50 years (23). Although familial inheritance of breast cancer cases was studied in North India, Karnataka, and Andhra Pradesh, no attempts to understand the status of familial breast cancer in Chennai has been done to date.

The breast cancer rates in the world are also influenced by environmental conditions such pesticides, higher consumption of fatty foods (red meat), and low consumption of fruits and vegetables (24,25,26). After diagnosis of breast cancer, increased consumption of fruits, vegetables, fish, low fat milk and soy-products was observed among the cases, which reduced the risk of breast cancer recurrence (27,28). Further, that adaptation of Western life style has led to an increase in the incidence of breast cancer in India. The life style factors such as older age at marriage, reduced breast feeding rates, and modern diets may be associated with the occurrence of breast cancer among younger populations in India (29,30).The Westernized life style, conserved genetic pool, higher frequency of consanguineous marriage, and older age at the time of marriage and childbirth are attributed to higher percentage of breast cancer among Parsis women

than women in other religious sects (31). Considering high prevalence of intra-caste marriages (consanguineous) in South India (6), our study aimed to discover patterns of familial inheritance, stages of breast cancer, and age shift, if any, among the breast cancer cases in Chennai, Tamil Nadu, India.

Materials and Methods:

To evaluate the familial and clinical stages of breast cancer, a case-control design was conducted, involving two groups, one group of breast cancer patients and a control group of age- matched women (non-cancer) from the same geographical area from February 2013 to January 2015. For this study, 512 breast cancer patients (cases) from different hospitals of Metropolitan City, Chennai were enrolled as the case group. For the control group, 540 age-matched, non-cancer women in and around Chennai were enrolled. Informed consent was obtained from all subjects that participated in this study. A well formulated English questionnaire was given to each patient, in both control and case group and their answers recorded. The patients who did not volunteer to respond to the questions were not included in this study. The questionnaire, originally written in English, was translated to regional languages for the patients who did not understand English language.

Preparation of questionnaire

The questionnaire was prepared in consultation with an oncologist to cover the family cancer, clinical stages of breast cancer, and other relevant information. General descriptions of the questionnaires and data collection procedures were followed-(32). The family history of breast cancer (whether their mother, father, grandmother, grandfather, aunt and uncle were affected or not) was noted. In the control group, women with familial cancer were excluded, and only women without any familial history were considered. The age of breast cancer diagnosis was taken into consideration. Similarly, the stage at which the cancer was diagnosed was recorded, which included TNM stages I to IV (33). Based on the available reports, the involvement of axillary lymph nodes (left or right breast), current treatment, period of treatment, and psychological counseling, if any, were noted from the medical history of breast cancer cases, and was approved by the Institutional Ethical Committee of the respective hospitals (Cancer Institute (WIA) Adyar, Chennai; Cancer Care Centre, Kumaran Hospital, Chennai and Kamatchi Memorial Hospital, Chennai)

Statistical analysis:

Data on the various risk-factors were collected from (breast cancer patients, n = 512) and controls (randomly selected non-breast cancerous women, n = 540) and were tabulated. Karl Pearson's chi-square test was performed to determine the overall association between a particular risk factor and breast cancer. When there was a significant association ($P < 0.05$), *post hoc* chi-square test (2×2 table) was performed (1) to compare any two categories of a risk factor and (2) to compare the proportion of breast cancer patients and the proportion of non-breast cancerous subjects in a specific category of a risk factor. *Post hoc* multiple comparisons of proportions were made by the Marascuilo's procedure and any absolute difference between two proportions (test statistics) that exceeds the critical value, r, was considered significant at that level of significance. All the calculations were performed either in Excel (34) or in Winpepi 11.43.

Results

Family history of cancer

The results of familial history of breast cancer in case and control women are presented in Table 1. Among the breast cancer cases, majority of them (86.72%) did not have history of the breast cancer in the family tree that included parents and close relatives. A similar trend was observed in the control women as well. Our study revealed that there is a statistically significant association between cancer history in the family and risk of breast cancer (χ^2:45.7464, p=<0.001). In those without any family history of breast cancer, the proportion of cancer history is significant, but significantly lower (χ^2:7.259, P=0.007), compared to those subjects where a history of breast cancer was present (χ^2:39.2, P=<0.001). These results indicate that the risk of getting breast cancer is significantly higher in women who had the family history of breast cancer.

Age at which breast cancer is diagnosed

Out of the 512 breast cancer patients evaluated, it was found that the age at which patients were diagnosed in the age groups of 41-45, 46-50 and 51-60 years are significantly higher compared to frequencies in 35-40 or 61-70 years age groups (Table 1). Women in the 46–50 and 51–60 age group had more breast cancer diagnoses in our investigation and the results are statistically significant (χ^2:60.6719, P=<0.001).

TNM Cancer stages

The stage of cancer diagnosis was recorded for the 512 women with breast cancer that were interviewed and the stage (I, II, III or IV) was recorded (Table 1). The present study revealed that the frequencies of breast cancer women with stage II diagnosis is significantly higher (46%) and the frequencies of patients with stage IV is considerably lower (χ^2:66.0912, P=<0.001). The order of cancer stages found among breast cancer cases were stage II > I > III > IV, respectively.

Axilliary Lymph nodes

Of breast cancer patients, the results revealed that the frequencies of breast cancer patients involving axilliary lymph node were higher (84%) than those who were negative (16%) (Table 1; (χ^2: 137.2137, P=<0.001).

Side of breast cancer (laterality)

Examining the occurrence of breast cancer in right side or on left side of breast (Table 1) revealed no statistical significance between the frequency of cancer patients having cancer on the left or on the right breast (χ^2: 1.2671, P=0.2602). However, our study showed 53.5% of patients had cancer in the left breast compared to 46.5% in the right breast among women with breast cancer in Chennai.

Types of treatment

Three strategies were used for treatment of breast cancer cases during the study period (Table 1). The treatments included chemotherapy (199 patients), followed by radiotherapy (169 patients), and surgery (144 patients). The results revealed that there is no significant difference between the three types of treatments and the number of patients in each treatment group among breast cancer cases, which include familial and non-familial types (χ^2:4.4396, P=0.1086).

Psychological counseling

The breast cancer patients, who are underwent treatment, were given psychological counseling to prevent stress among the patients (Table 1). The frequency of cancer patients that received psychological counseling (57%) was marginally higher than that of no-counseling group (43%).

Period of treatment

Out of the 512 breast cancer patients analyzed, the ranges of treatment time varied from less than 6 months to 12 months or more (Table I). There are significant differences between the time periods of treatment among the breast cancer cases (χ^2: 103.35, P<0.001). Further, the frequency of cancer patients that underwent treatment for less than 6 months (chemotherapy) was higher compared to those cases that underwent treatment for 12 months or more (chemotherapy, surgery and radiation).

DISCUSSION

India is a country with different ethnic religions, cultural, economic status, and health care systems. Breast cancer inheritance is present in 5 – 10% of those with breast cancer and multiple factors including variations in geographical regions racial, life style, and environmental factors are involved in the onset of breast cancer (35). The outcome of our study highlighted that factors other than genetics are contributing the genesis of breast cancer. The study of familial cancer is useful in order to assess a woman's risk for developing breast cancer, creating prevention and treatment methods, and developing future planning strategies. The Madras Metropolitan Tumor registry has shown that breast cancer incidence rates are increasing worldwide, and therefore, there is an urgent need to develop strategies for prevention (36,37).

The results of this study revealed that 13.28% of cases had the family history of breast cancer and 2.2% of controls women had family history of cancer among the women in Chennai. There was strong significant association between breast cancer history in the family and the diagnosis of breast cancer (P<0.001). However, in Chennai's population, the proportion of cancer patients with no hereditary origin is also statistically significant (χ^2: 7.259, P<0.007) indicating that other factors besides genetics is involved in breast cancer. In comparison, Shangai had lower (3.2%) cases with family history of breast cancer (38). In developing nations like Bahrain (39) and Malaysia (40), family history showed increased risk for breast cancer in 20% and 16% of

cases, respectively. A positive association between family history of cancer and risk of breast cancer was also reported in the studies of Japanese women (41), Iranian women (42), and in the Cyproit (Eastern Mediterranean country) population (43).

According to the 1992-1993 National Family Health Survey (NFHS) that was conducted, consanguineous marriage has dropped from 12.9% to 11.9% in India. In Mangalore (Karnataka) 12.3% of consanguineous marriage was reported in urban areas (44). The highest rate of consanguineous marriage was reported in Tamil Nadu (38%), followed by Andhra Pradesh (30.8%) and Karnataka (29.7%). Further, higher rates of consanguineous marriage were observed in rural areas (45) and notably, in the present study, breast cancer rates were also observed to be significantly higher in rural women than in urban women in Chennai. In this context, it is inferred that where there is higher percentage of intra community marriage (38% in Tamil Nadu and 30.8% in Andhra Pradesh), there was a higher percentage of breast cancer with hereditary origin of 13.2% in Chennai as observed in the current study, and 17% in Andhra Pradesh (13), implying that there is a circumstantial relationship between intra community marriage and occurrence of hereditary breast cancer. In New Delhi, where a low percent (4.3%) of consanguineous marriage was recorded, a higher percentage of (20.7%) hereditary breast cancer was reported that may be attributed to genetic mutations from exposure to chemicals in urbanized and industrialized settings (16).

The low rate of familial pattern of breast cancer in the Indian patients has been reported by many researchers (2). Further, in most populations, 6–10% of patients with cancer have mutations in BRCA gene, irrespective of family history. Nevertheless, a number of Indian studies pertaining to germ line mutation analysis of BRCA 1 and BRCA 2 genes in breast cancer reported that BRCA mutation makes up 9–25% of familial breast cancer cases (9,46,47,48). Three novel BRCA1 mutations including the founder Ashkenazi BRCA1 mutation have been reported in breast cancer patients in India **(**48). Studies have shown that 60% breast cancer family cases with site-specific female breast cancer cannot be explained by BRCA 1 and BRCA 2 (49,50). Moreover, population studies have demonstrated that these genes only account for 15% of the overall familial risk of breast cancer (51). These studies revealed that very low proportion of breast cancer cases are due to genetic inheritance further proving that other factors are involved in the genesis of non-familial breast cancer. Although it has not been verified, one may draw the conclusion that the human genetic profile has not changed over the past 10,000 years, whereas major changes have taken place in our food supply, energy expenditure, and physical activity (52).

In our investigation, the risk for breast cancer in age groups, 41-45, 46-50, and 51-60 are significantly higher than the age groups 35-40 or 61-70 among breast cancer cases in Chennai ($P<0.001$). A peculiarity is that there is shift in the age group of women affected by breast cancer from 45 to 50 to 35 to 45, which indicates that young women are more affected by breast cancer and coincides with other studies (53). The mean age of breast cancer diagnosis was 47.73 years in Delhi (11), 40 years in Chennai and Trivandrum (54), and 48 years in North Karnataka (14). In Chandigarh (a union territory of India), the rates of breast cancer in those less than 40 years of age was 34%, followed by 23% in the 41-45 age group, 7.4% in the 46-50 age group, and 25.3% in the 50 plus years age group (10). Chopra et al (15) reported higher proportions of breast cancer in the age group of 41–50 years and less in 51–60 years in Punjab state, India. The incidence of breast cancer in women younger than 35 years is rare and it represents 2% of all cases in the Western population. However, the incidence of younger women affected has increased in the Indian population. For instance, breast cancer incidences in younger women <35 years of age has been reported in Bangalore at11.25%, (53) and in New Delhi at 5.5%, and 8% (55,56).

In our study, the frequencies of breast cancer patients with stage II (46%) was significantly higher followed by stage I (23%), III (21%), and stage IV (10%). In Haryana, 42.2% of cancer diagnoses presented in stage IV, and it is attributed to lack of literacy of breast cancer risk factors among the study population (57). Meshram etal., (58) reported more than 90% were in the late stages of breast cancer in Nagpur (Maharashtra). Similar late stages of (III and IV) of breast cancer were reported in Manipal (Karnataka) (59) and in Kerala (60).

In Brazil, rates of stage II breast cancer was 42.5%, followed by stage I (32.5%), and stage III (20%) (61). Similar trends of incidence were reported in Singapore (62). In Iran, 50% of the breast cancer cases were diagnosed in a stage III, 30% in stage II, 5% in stage I, and 5% in stage IV (63). Our findings of breast cancer in stages I, II, and III are in agreement with the above reports. Therefore, it is suggested that an awareness and screening program for early detection of breast cancer in women is created, which may aid in higher curative rates with shorter treatment time periods, thus resulting in higher survival rates.

In our study, the positivity of axillary lymph node in breast cancer cases was significantly higher than the negative cases and the results are in concurrence with the other reports (64,65). A similar observation of lymph node involvement was reported in New Delhi, India (16) and in Tirupati (A.P) (13). In Singapore, 35.8% of cases were found to be node positive and the percent of breast cancer varies with different races, 86.1% in Chinese, 8% in Malay, 4.0% in Indian, and 1.9% in other races (62).

Our study revealed that most patients had breast cancer on left side (54%) than right side of breast (46%), which are in concurrence with the other studies (14,64,66) and is attributed to the bulkier characteristics of the left breast in which the upper outer quadrant has a relatively larger volume of breast tissue compared to right breast (22). Similar trends in the rate of cancer in the left-side of breast were reported in women in several countries including Turkey (67), Iran (63), Iceland (68), and in Egypt (69). Three types of treatment namely viz., chemotherapy, radiotherapy, and surgery were commonly noted among breast cancer patients in our study and a similar types of treatment have been noted among breast cancer patients in other studies (54,61,62,63).

The stress due to cancer, household problems, and in the workplace was significantly noted among the breast cancer cases. Hence it is suggested that practicing yoga, meditation, and having a daily routine for physical exercise to overcome the stress in breast cancer cases is needed. Further, the patients enrolled in this study attended breast cancer survivor meetings to get both psycho- oncological counseling and treatment. It is therefore suggested that routine counseling sessions may be necessary to avoid any further complications. Overall, breast cancer cases undergoing treatment for less than 6 months was higher than the patients who are treated more than 6 months based on the stages of breast cancer and types of treatment (chemotherapy, surgery and radiation).

Due to the risk of cancer found in both those who had a family history of cancer and those who did not, life style factors such as dietary habits, smoking, alcohol consumption and infection, may have a profound influence on development of cancer and imply that many types of the cancers are not due to hereditary factors (20,70). According to Doll and Peto (24), only 5-10% of all cancer cases are due to genetic defects and the remaining 90-95% is due to environment and lifestyle and suggested that cancer deaths can be prevented by modifying the diet. Epidemiological studies implicate that a western diet and/or westernization of diet act as a probable cause of the increasing incidence in breast cancer in India (71). It has been suggested that vegetarian diets are inversely related to overall cancer incidence (72). Vegetarian diets seem to confer protection against cancer and specifically the risk of female specific cancers when compared with non-vegetarian diets (73). It is, therefore, concluded that modification of lifestyle and food habit may need to study in order to determine its role in preventing the risk of breast cancer, as the majority (87%) of breast cancer diagnoses were not due to genetic inheritance.

Conclusion:

Our study suggests that familial breast cancer is very low in the female population in Chennai and the results are in line with the many studies globally. The results of investigation imply that genetic inheritance of breast cancer is limited to 5-10% and the non-genetic factors such as environments, dietary habits, and lifestyle factors may play a role in genesis of breast cancer. Early screening and awareness programs for women along with diet, counseling, and an integrated preventive approach may decrease the rates of breast cancer in the future.

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Declaration of Conflict of Interest:
The authors declare no conflicts of interest.

Table 1: Studies on Familial cancer and clinical stages of breast cancer cases and control women in Chennai.

S. No.	Study groups		Cases (n=512)		Control (n=540)		χ^2	P value
			Frequency	%	Frequency	%		
1	Cancer history	No cancer history in family	444	86.72	528	97.80	45.74642	P<0.001
		Breast cancer history	68	13.28	12	2.20		
2	Age at breast cancer was Diagnosed (Years)	35 – 40	39	7.62	–	–	60.67119	P<0.001
		41 – 45	119	23.24	–	–		
		46 – 50	144	28.13	–	–		
		51 – 60	154	30.08	–	–		
		61 – 70	56	10.94	–	–		
3	Cancer stages	I	118	23.05	–	–	66.09129	P<0.001
		II	234	45.70	–	–		
		III	109	21.29	–	–		
		IV	51	9.96	–	–		
4	Axiliary lymph nodes	Positive	432	84.38	–	–	137.2137	P<0.001
		Negative	80	15.63	–	–		
5	Side of cancer	Left	274	53.52	–	–	1.267191	P=0.2602
		Right	238	46.48	–	–		
6	Types of treatment	Chemotherapy	199	38.87	–	–	4.439691	P=0.1086
		Radiotherapy	169	33.01	–	–		
		Surgery	144	28.13	–	–		
7	Psychological Counseling	Yes	292	57.03	–	–	5.087653	P<0.001
		No	220	42.97	–	–		
8	Period of treatment (Months)	<6	273	53.32	–	–	103.335	P<0.001
		7 – 12	197	38.48	–	–		
		Above12	42	8.20	–	–		

Note: '–' = Not applicable; Controls are free from breast cancer, hence, S. No. 2 to 8 are marked as NIL

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