Original Article

Risk Factors for Breast Cancer among Indian Women: A Case–control Study

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ABSTRACT

Background: Breast cancer is the most common malignancy among females all over the world. The incidence of breast cancer is persistently on the rise due to urbanization and lifestyle changes. Although various risk factors have been suggested for estimating the risk of developing breast cancer, most of these have been studied in the Western population. A better understanding of local characteristics of risk factors may help in devising locally effective prevention strategies for breast cancer. The primary objective of the study was to study the risk factors for carcinoma breast among Indian women. **Materials and Methods:** This was a case–control study, conducted from January 2011 to December 2012, at a tertiary level teaching institution. A total of 100 patients of Indian origin, attending the General Surgery Department with carcinoma breast during this period were the cases. Controls were the blood relatives of patients with other diagnosed malignancies. **Results:** The major risk factors for breast cancer are found to be age, diet, waist size, hip size, waist-hip ratio (WHR), body mass index, high-density lipoprotein cholesterol, triglyceride, more than three pregnancies, number of years of menstruation, atypical hyperplasia in the previous biopsy, and history of carcinoma in relatives. **Conclusions:** Waist size and WHR are the major risk factors for carcinoma of breast. Adequate exercise and weight control are the most effective lifestyle changes that can reduce the risk of developing breast cancer.

KEYWORDS: *Breast cancer, case–control study, risk factor, waist-circumference, waist-hip ratio*

INTRODUCTION

Breast cancer, with its uncertain cause, has captured the attention of surgeons throughout the ages. Breast cancer is the second most common cancer in women worldwide with 1.05 million new cases being estimated in the year 2010. It attains significance in being a major determinant of both morbidity and mortality in the affected female population. Even among females in India, the incidence of this disease is ever on the rise, due to urbanization and subsequent change in lifestyles. All women are at risk for breast cancer, with the risk increasing with age. Breast cancer cannot be fully prevented, but it can be effectively treated and even cured if detected early. Anything that increases the chance of developing a disease is called a risk factor.

Population-based studies have shown that reproductive factors, including early menarche, late menopause, nulliparity, and absence of a history of breastfeeding increase the risk of breast cancer.[1] Several lifestyle-related risk factors have also been shown to contribute to breast cancer development, including lack of physical activity, overweight, smoking, alcohol usage, oral contraceptive usage, hormone replacement therapy, poor dietary intake, and radiation exposure.[2] In addition, studies of families with high breast cancer incidence have shown that about 5%–7% of breast carcinomas are hereditary.[3]

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There is a four to fivefold variation in breast cancer incidence rates across different countries. The lowest rates are observed in Asia, and the highest rates are observed in Western Europe and North America. The incidence of breast cancer has increased in all countries since 1960. Some groups studied in detail, the changes in incidence and mortality between 1955 and 1990 in four age groups (35–44, 45–54, 55–64, and 65–74) for 11 representative countries (the USA, England, Norway, Hungary, Yugoslavia, Spain, Colombia, Singapore, Japan, India, and China).[4] The largest increase in incidence took place in Japan and Singapore. The incidence rate for women aged 35–44 in Japan doubled between 1960 and 1985 and by 1985 was roughly two-thirds the USA rate. There has been essentially no change in mortality rates in the USA, England, or Norway whereas there has been a 50%–60% increase in Japan, Singapore, and Hungary. Most of the observed increase in incidence rates in the USA, England, and Wales and Norway may be spurious, due to changes in screening patterns. Screening may also have contributed to the rate increase in other countries, but outside Western Europe and North America, the major part of the increase is likely to be due to changes in known and suspected breast cancer risk factors. Breast cancer incidence has been rising rapidly in Japan, surpassing uterine cancer in frequency. In several Chinese cities, breast cancer incidence has increased substantially in recent decades.

Carcinoma breast is the second most common cancer among Indian women, and an increasing trend in its incidence has been observed in most of the metropolis with Mumbai topping the list. Based on the cancer registry data, it is estimated that there will be about 800,000 new cancers cases in India every year. At any given point, there is likely to be 3 times this load: that is about 240,000 cases. The incidence of breast cancer increased by approximately 50% between 1965 and 1985.[5] Much of this increase may be associated with increasing urbanization and improved life expectancy. The incidence rates, education level, and income are higher in urban areas compared with rural areas. In addition, age at puberty and pregnancy-related factors, such as parity, age of first childbirth, and number of children, are factors possibly related to breast cancer.[6]

There is clear scientific evidence linking several factors with breast cancer risk. These factors are the so-called "established" risk factors for breast cancer. Some are inherited predispositions while others are aspects of a woman's lifestyle or reproductive history. The established risk factors for breast cancer include female gender, age, previous breast disease, family history/genetic risk factors, early age of menarche, late age of menopause, late age of first full-term pregnancy, postmenopausal obesity, lack of physical activity, and exposure to high-dose radiation.[7-10]

The Breast Cancer Risk Assessment Tool is based on a statistical model known as the "Gail model," which is named after Dr. Mitchell Gail, Senior Investigator in the Biostatistics Branch of NCI's Division of Cancer Epidemiology and Genetics.[11] The model uses a woman's own personal medical history. The Gail model has been tested in large populations of caucasian women and has been shown to provide accurate estimates of breast cancer risk. The model still needs to be validated for Hispanic women, Asian women, and other subgroups. In addition, the results need to be interpreted by a health-care provider for women with special risk factors, such as women who are carriers of gene mutations.

Other risk factors such as age at menopause, dense breast tissue on a mammogram, use of birth control pills or hormone replacement therapy, high-fat diet, alcohol drinking, low physical activity, obesity, or environmental exposures, are not included in risk estimates with the Breast Cancer Risk Assessment Tool. They are excluded because the evidence is not conclusive or researchers cannot accurately determine how much these factors contribute to the calculation of risk for an individual woman, or adding these factors decreases the accuracy of the tool appreciably. The inclusion of newer factors such as breast density and other modifiable risk factors is powering the ongoing evolution of breast cancer prediction tools.

Substantial advances have been made in the treatment of breast cancer, but the introduction of effective methods to predict women at elevated risk and prevent the disease have been less successful. International variation in both incidence and mortality is supposed to be one of the most striking reasons for this conundrum. With this background, this study was undertaken to study the modifiable risk factors for breast cancer in Indian background. The primary objective of the study was to study the risk factors for carcinoma breast among women of Indian origin.

Materials and Methods

This case–control study was conducted between January 2011 and December 2012 at the study institution, which is one of the largest public sector health-care centers in the state. The protocol was approved by the Institutional Review Board of and approved by the Ethics Committee of the research institution.

Cases included female patients of Indian origin, diagnosed to have carcinoma breast, attending the Outpatient department and those admitted in the surgical wards during the study period. Controls included females of Indian origin, who were the attendants of patients admitted with other malignancies in the same ward.

Exclusion criteria for cases

Diagnosed gynecological malignancies, age <20 or more than 70, advanced stage with cachectic symptoms.

Exclusion criteria for controls

Any diagnosed malignancies, age <20 or more than 70, blood relative of a patient having breast cancer.

The results of a similar study were used to calculate the sample size for the present study. A sample size of 100 cases and 101 controls was found to be adequate to test the significance.

All the cases and controls who satisfied the inclusion and exclusion criteria were included in this study, after informing them about the details of the study and obtaining informed written consent in the subjects' own language. The questionnaire was filled after interviewing the study group. Morphological assessment was done, and details were entered. Blood investigation of fasting lipid profile was sent, and the values were entered during follow-up. All cases were subjected to the routine investigations and usual management.

The questionnaire consisted of details including:

a. Demographic details such as name, age, residence, and education status
b. Personal details like diet, smoking, etc.
c. Menstrual history such as age of menarche, regularity of cycles, months of menstruation, and menopause details
d. Pregnancy and lactation details such as age of first pregnancy, weight during pregnancy, no of live birth, abortions, and duration of lactation
e. Family history of any carcinomas
f. Morphological assessment such as height, weight, body mass index (BMI), and waist-hip ratio (WHR)
g. Fasting lipid profile values
h. Details of biopsies done on breast.

After collecting data using the questionnaire, they were entered into a sheet in Microsoft Office Excel 2007. Statistical analysis was done using the software SPSS version 16 (IBM Inc, USA). All relevant data are presented as mean ± standard deviation. The data were analyzed using *t*-test, Chi-square test, and ANOVA as appropriate. Those risk factors found to be independently significant were analyzed in detail. $P < 0.05$ was considered to be statistically significant wherever applicable.

Results

The study group consisted of 100 cases and 101 controls, all of them females. The study participants comprised cases in the age range of 23–72 years and controls in the range 21–74. The mean ages were 50.85 and 45.74 for cases and controls, respectively. The lowest age of a patient with carcinoma breast was found to be 23 years. Fifty-six percent of the cases and 57% of the controls came from rural areas. About 18% of cases and 9% of controls were illiterate. Seventy-three percent of cases and 51% of controls were nonvegetarians. Ten percent of both cases and controls were vegetarians.

Among cases, the mean height was 155.94 cm, mean weight was 64.01 kg, and the mean BMI was 26.19. The mean waist circumference was 91.46 cm while mean hip circumference was 96.24 cm. Among controls, the mean height was 157.52 cm and mean weight was 63.75 kg while the mean BMI was 25.7. WHR was calculated as waist circumference (in cm) divided by hip circumference (in cm) as a measurement of fat distribution that reflects adipose tissue and muscle mass. The mean waist circumference was 82.78 cm while mean hip circumference was 99.35 cm [Table 1]. Fifty-one and 28 of the patients with carcinoma breast had WHR of 0.9–1 and >1, respectively, when compared to 15 and 4 of controls, respectively [Table 2]. Thirty-nine percent of the cases were obese before the onset of carcinoma breast.

Forty-two percent of cases and 58% of controls were found to have exposure to smoking, all of them passive. Eighty-five percent of cases and 70% of controls were married. The mean age of menarche was 13.57 for cases and 12.79 for controls. The mean duration of menstruation was 341.5 months in cases and 314.9 in controls among the study group. Nearly 89% of cases and 82% of controls had been pregnant before. Twenty-two percent of cases and 10% of controls were found to have more than 3 pregnancies. Age at first child

Table 1: Anthropometric features among cases and controls

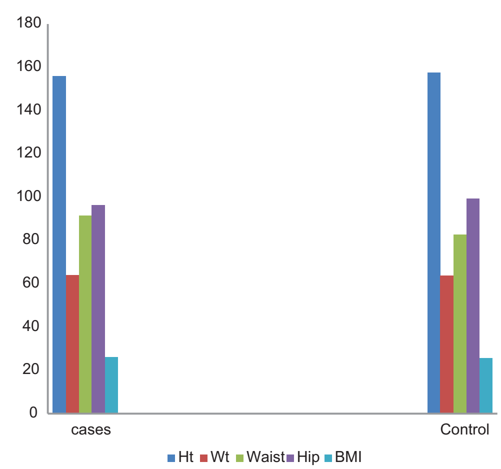
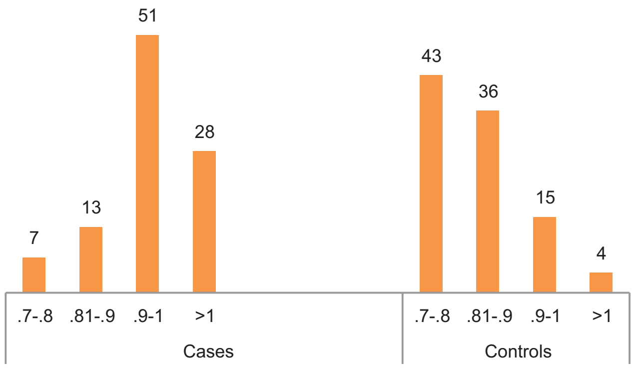


Table 2: Waist-hip ratio among cases and controls



birth was calculated by subtracting the age of onset of menarche from age of the first live birth. Mean age among cases were 10.5 years and that among controls were 11. Eighty-four percent of cases and 75% of controls had history of breastfeeding, with no significant difference in the frequency among cases and control, when compared using Chi-squared test. About 55% of cases and 47% of controls were postmenopausal.

There were five cases with a history of atypical hyperplasia in the previous biopsy whereas none in controls. About 11 cases had first-degree relatives with history of carcinoma whereas only two among controls had such a history. Much lesser amount of physical activity found more among cases. The mean value of total cholesterol was found to be 221.2 in cases and 215.73 in controls. The means of low-density lipoprotein cholesterol were 147.12 and 149.2 in cases and controls, respectively. Means of high-density lipoprotein (HDL) were 39.14 in cases and 42.8 in controls. Triglycerides showed a mean of 163.38 in cases and 151.58 in controls.

Discussion

At the end of the study, the various parameters were analyzed statistically to test the research questions. Using *t*-test, age was found to have significant difference among cases and controls ($P = 0.000$). As per literature, only age and BRCA carrier status are associated with larger relative risks of breast cancer than percent mammographic density (PMD).[12] With regard to rural-urban distribution, no significant difference was noted among cases and controls when distribution was tested with Chi-squared test. This finding was in contrary to some previous studies which said that breast cancer was more prevalent in urban areas.

According to Helmrich *et al*., 12 years of education were an independent risk factor for development of breast cancer.[13] However, such a finding was not obtained in the present study, even though there were a substantial number of graduates and postgraduates among the controls.

Nonvegetarians and eggetarians were having higher occurrence of carcinoma breast than vegetarians. Using one-way ANOVA test, significant difference was found in dietary habits among cases and controls. A randomized trial performed by the WHI of reduction of the proportion of fat in the diet resulted in a nonsignificant 8% reduction in the risk of breast cancer, but they found some confounding with weight loss.[14] There was no advantage to an increase of fruit and vegetable intake in another large randomized adjuvant trial.[15] A systematic review of diet and breast cancer was performed by Albuquerque and colleagues, who concluded that a Mediterranean dietary pattern and diets composed largely of vegetables, fruit, fish, and soy are associated with a decreased risk of breast cancer. Risk reduction may also be helped by appropriate intakes of dietary fiber, fruits, and vegetables.[16,17]

BMI was found to be significantly different in cases and controls, with the prevalence of overweight and obese patients higher among cases ($P = 0.004$). Strong observational data indicate that weight gain in the premenopausal period and being overweight or obese after menopause increase breast cancer risk. Greater birth weight and adult height also have been shown to be positively associated with PMD and increased risk of breast cancer.[18,19] In a meta-analysis, Renehan *et al*. estimated that for each 5 kg/m^2 increase in BMI the risk of breast cancer was increased by 12%.[20]

When comparing the various anthropometric parameters using *t*-tests, only waist circumference and hip circumference were found to be significantly different among cases and controls ($P = 0.003$). Waist circumference also estimates abdominal fat and is strongly correlated with BMI.[21] The ratio of the WHR has been the most frequently used measurement to assess body fat distribution with upper body, or central obesity being represented by a high ratio. However, waist circumference is considered a better indicator of the visceral adipose tissue and a better predictor of breast cancer risk than WHR.[22] Several large prospective studies, including the Nurses' Health Study and the European Prospective Investigation of Cancer and Nutrition study, observed that larger waist circumference was associated with an increased breast cancer risk.[23,24] Several other studies that assessed metabolic syndrome in relation to breast cancer risk also found an association with central obesity.[25]

No significant difference was found among cases and controls when compared using Chi-squared test in smoking exposure. No significant difference was found among cases and controls when assessed for marital status also. According to Gajalakshmi and Shanta, single women had more risk than married women.[26] However, such a finding was not obtained in the present study. The mean age of menarche was 13.57 for cases and 12.79 for controls, which was found to be significantly different when compared using *t*-test ($P = 0.004$). The importance of age of menarche and age of the first child birth was to identify the duration of unopposed cycles which when more than 12 years posed a significant risk for development of breast cancer as per Gajalakshmi and Shanta.[26] Using Chi-squared test, duration of menstruation was found to be significantly higher in cases than in controls (P =< 0.000). Age at first childbirth was not found to be an independent risk factor for carcinoma breast. The scientific hypothesis behind age of menarche and age of the first live birth can be explained as the duration of unopposed cycles. The risk for carcinoma breast increased with advancing age of menopause as noted by many authors. The present study corroborates the finding that increased the duration of menstruation is associated with a higher risk of developing carcinoma breast.

There was a significant difference in the frequency of females with no history of pregnancy among the cases and controls ($P = 0.004$). Nulliparous females had more risk of developing carcinoma breast, about 3-fold risks as suggested by various studies. Also, number of pregnancy was found to be a significantly lower when compared with the controls using the Chi-square test ($P = 0.010$). This finding agrees with various previous studies which say that high number of parity was associated with a reduction in the risk for developing carcinoma breast. There was no significant difference noted in the number of abortions among cases and controls. This finding agrees with the study by Rao *et al*., in which abortion did not emerge as a risk factor for the development of carcinoma breast.[27] However, there are other scientific studies available, which indicate that abortion, especially induced abortion increased the risk of developing carcinoma breast.

Eighty-four percent of cases and 75% of controls had history of breastfeeding, with no significant difference in the frequency among cases and control, when compared using Chi-square test. However, there was a significant difference between the duration of lactation among the cases and controls, when tested using independent *t*-test ($P = 0.002$). Compared to those who never breastfed their children, those who breastfed their children had a significant protection and this protection increased with the duration of breastfeeding. This agrees with many previous studies that a longer duration of breastfeeding reduces the risk of breast cancer. The Collaborative Group on Hormonal Factors in Breast Cancer estimated in 2002 that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women, by age 70, if women had on average more children and breastfed for longer periods as seen in developing countries.[28]

When the prevalence of postmenopausal and premenopausal women among cases and controls was compared, a significant difference was noted. This finding was consistent with the study of Reddy. who said postmenopausal women were more at risk for developing breast cancer than premenopausal women.[29] Estrogens may explain the increased risk of breast cancer in obese postmenopausal women although this does not preclude other hormones and cytokines from mediating the effects of estrogen or other mechanisms by which obesity might affect cancer risk.[30]

There were five cases with a history of atypical hyperplasia in the previous biopsy whereas none in controls, which was found to be significantly higher ($P < 0.000$), when compared using Chi-squared test. This agreed with the previous studies which quote that number of breast biopsies and history of atypical hyperplasia increased the risks of developing breast cancer. About 11 cases had first-degree relatives with history of carcinoma, whereas only 2 among controls had, which was found to be significantly higher ($P = 0.002$). This is in agreement with many studies which say that the presence of first-degree relative with breast cancer increases the risk of developing breast cancer. However, some studes, like the one by Reddy note that family history was not a risk factor for the development of breast cancer.[29]

When the levels of physical activity were tested using one-way ANOVA, there was a significant difference in the levels of physical activities with lesser physical activity found among cases ($P = 0.004$). This finding suggests that higher physical activity reduces the risk of developing breast cancer. A recent review suggests that half of breast cancer cases may be prevented if the major modifiable risk factors, including achieving and maintaining a healthy weight, regular physical activity, and minimal alcohol intake, are instituted.[31] The World Cancer Research Fund/American Institute for Cancer Research has estimated that over 40% of postmenopausal breast cancer could be prevented by reductions in alcohol, excess body weight, and inactivity.[32]

When the means of lipid profile were compared using independent t-tests, significant differences were found only in the HDL and triglycerides values among the cases and controls. Higher HDL levels and lower triglyceride levels were associated with decreased risk of developing breast cancer. Although some case–control studies have reported a positive association between HDL cholesterol and breast cancer risk, prospective studies have reported either no association or an inverse association with breast cancer risk.[33-35] Some studies examined the associations of HDL by menopausal status, but those results are also inconsistent.[36,37] Low HDL cholesterol level measured at baseline was not associated with breast cancer in the WHI or in women ≥50 years old in the Me-Can study, but the Atherosclerosis Risk in Communities cohort and one Norwegian cohort study observed that low HDL cholesterol levels are significantly associated with a 30% and 67% increased risk of breast cancer, respectively.[36-39] The Me-Can study also reported that low HDL is inversely associated with breast cancer in women under 50-year-old.

The variables showing significant odds ratio in crude analysis were selected for further testing with binary logistic regression. Thirteen variables satisfied this criterion in crude analysis. These variables were entered for binary logistic by Enter method to study the adjusted odd ratio. It may be noted that the variable lactation which lost significance after binary logistic regression was excluded for further calculation, and those variables that remained significant after adjustment were taken for modeling using backward step-wise method. Those are age, diet, waist size, hip size, WHR, BMI, HDL cholesterol, triglyceride level, more than three pregnancies, number of years of menstruation, atypical hyperplasia in the previous biopsy, carcinoma in relatives.

At the end of logistic regression analysis, the variables that remained independently associated with the dependent variable were age, diet, waist size, hip size, WHR, BMI, HDL cholesterol, triglyceride level, more than three pregnancies, years of menstruation, atypical hyperplasia in the previous biopsy and history of carcinoma in relatives.

Conclusions

This study has some limitations. First, it was hospital-based rather than community-based, so the cases may not be entirely representative of all Indian women with breast cancer. However, population-based disease surveillance systems are deficient in the country, as the population is large and spread over a vast area. There is as yet no large-scale, geographically representative study of breast cancer risk factors among the general population. Second, we were unable to control for all potential confounders in the association of risk factors with breast cancer. Other limitations of the study include the fact that hereditary factors which are major risk factors were not included in the study. Recall bias could be very high because of the nature of the study design. In addition, age-stratified analysis, if done, could have been better-suited to study the risk factors.

However, we do reiterate the fact that we have been able to point out the risk factors for developing breast cancer in Indian women. Further studies are needed to validate the present model, and then, it can be used for identifying high-risk women, who can be kept on regular follow up as well as offered early treatment options. Our findings indicate that primary prevention strategies, including health education and policy modification, might prove useful. Future prospects for the application of these risk factors include improvements in mammographic screening, risk prediction in individual groups, cancer prevention as well as clinical decision-making.

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Conflicts of interest

There are no conflicts of interest.

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