STUDY OF KNOWN RISK FACTORS IN BREAST CANCER PATIENTS IN THE REGIONAL POPULATION

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ABSTRACT

BACKGROUND

Breast cancer was the most common cancer in India in 2018. It also caused the most cancer related deaths in India in 2018. In order to decrease the mortality from breast cancer, it is essential to identify the population at risk, and diagnose breast cancer at an early stage. However, breast cancer risk factors have been studied mostly in European and American countries whose traditions, practices, habits and lifestyles are enormously different. Even within a country like India there is vast diversity with respect to various cultures, traditions and practices. Hence the risk factors for all these diverse groups may not be the same. We wanted to study the known risk factors in breast cancer patients in the regional population.

METHODS

This is a cross sectional study of 100 women with a histopathological diagnosis of breast cancer who presented to Government Medical College, Amritsar.

RESULTS

Breast cancer presented at an earlier age 52.02 ± 9.42 and at a later stage compared to other developed countries. 40% of the patients had no risk factors for breast cancer. The most common risk factor was BMI ≥ 25 in 40% cases. Life style related risk factors- alcohol and smoking were present in 4% cases. Risk factors related to estrogen exposure were early menarche (1%), nulliparity (1%), lack of breast feeding (0%), OCP intake (6%), late menopause (4%), HRT (0%). Family history of breast cancer was present in 1%. None of the cases had significant radiation exposure prior to diagnosis.

CONCLUSIONS

The risk factor profile for breast cancer in the Indian population differs from that of other countries in whom the risk factors were first identified and studied. Hence a large multicentre study is required to identify the risk factors relevant to the Indian population.

HOW TO CITE THIS ARTICLE: Kumar A, Tirkey ABK, Singh S, et al. Study of known risk factors in breast cancer patients in the regional population. J. Evolution Med. Dent. Sci. 2019;8(18):1446-1450, DOI: 10.14260/jemds/2019/322

BACKGROUND

In 2018, breast cancer has been the most common cancer across all ages and both sexes with 1,62,468 new cases reported in the year. It has the highest 5-year prevalence among all cancers in India which is 4,05,456 cases. It has also been the most common cause of cancer related death with a mortality of 87,090 cases in 2018.¹ Hence breast cancer is an alarming nationwide health problem of an ominous magnitude causing great morbidity and mortality.

In spite of the magnitude of this problem, there is no national screening programme for breast cancer.² the mean age of presentation of breast cancer in the United States of America is 62 years whereas in India it is 50 years of age.^{3,4} A vast proportion of the population still lives in the rural area and are uneducated. They tend to present late with the disease due to inaccessible health care, cost, lack of knowledge or social stigma.⁵ Even in the urban population, practices like self-breast examination are uncommon.

'Financial or Other Competing Interest': None.
Submission 16-03-2019, Peer Review 20-04-2019,
Acceptance 26-04-2019, Published 06-05-2019.

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DOI: 10.14260/jemds/2019/322

This leads to late presentation where the treatment may not be as successful as early breast cancer.

It is important to identify the risk factors present among individuals. This will enable early screening and diagnosis among this population which is at an increased risk for breast cancer. The risk factors commonly implicated for breast cancer are factors related to oestrogen exposure- early menarche (≤ 11 years), nulliparity, lack of breast feeding, intake of oral contraceptive pills, late menarche (≥ 55 years), use of hormone replacement therapy. Life style related risk factors are – smoking, alcohol, night shift work, BMI ≥ 25 and lack of physical activity. Family history of breast cancer and exposure to therapeutic radiation are also important risk factors for breast cancer.

India is a country with vast differences in cultures and practices within the country itself and from the Western civilization. Hence the risk factors for breast cancer may not be the same as for them. This study aims to find the prevalence of these known risk factors among breast cancer patients in the regional population.

METHODS

This is a cross sectional study conducted in Government Medical College, Amritsar where 100 females with histopathological diagnosis of breast cancer were selected by convenience sampling. Any female patient with breast cancer who consented for the study was eligible for selection.

A questionnaire based one on one interview was undertaken where the following information was obtained. Demographic variables obtained were age, educational status, occupation and marital status. BMI was calculated using height and weight of the patient. Questions related to breast cancer risk factors were asked about age of menarche, number of children, age at first child birth, breast feeding, intake of oral contraceptive pills, age at menopause, use of hormone replacement therapy. Questions about lifestyle related risk factors like night shift work, lack of physical activity, smoking and alcohol intake were also asked. Questions related to family history included any first degree or second degree relative with breast cancer in the family. Information about any exposure to therapeutic radiation was also obtained in the questionnaire. Other disease related information obtained were stage at diagnosis, histological diagnosis, ER/PR and Her-2/neu receptor status.

The data obtained was entered into excel sheet, and analysis was done with the help of excel functions and is presented here as mean and percentages. Since the risk factor assessment is based on the verbal responses that involve recalling information of several years back, the possibility of memory recall bias cannot be ruled out.

The study was carried out between January 2017 and July 2018 after approval from the institutional ethics committee.

RESULTS

The mean age at presentation was 52 ± 9.42 years with 12% presenting between 30-40 years of age, 22% between 41-50, 56% between 51-60, 8% between 61-70 and 2% cases > 70 years of age. The youngest case was 32 years old and the oldest case was 85 years old.

20% of the cases were illiterate, 17% had completed primary education, 24 % had completed middle school education, 25% had completed matric and 14% had studied beyond matric with only 1% having completed post-graduation. 88% of the cases were housewives, 4% were teachers and labourers each, 2% were clerks, 1% had a government job and 1% had tailoring as her occupation. None of the cases were in occupations involving night-shift work.

The mean BMI of the patients was 24.85 ± 2.98 . 60 % of the cases had BMI < 25, 35 % had BMI between 25-29.9 and 5 % cases had BMI ≥ 30 . 22% of cases lacked exercise or moderate physical activity in their daily routine. 4% of the cases, labourers by occupation had a history of consumption of alcohol and smoking whereas 96 % cases had never smoked or consumed alcohol.

21% of the cases had presented at stage IIa, 32% at IIb, 28% at IIIa, 17% at IIIb and 2% at stage IV of the disease. None of the cases presented at stage I. Most common histological sub type was infiltrating ductal carcinoma (84%). Other histological subtypes were infiltrating lobular carcinoma (5%), papillary carcinoma (9%), medullary and micro-papillary, each 1%.

The mean age at menarche was 14.23 ± 1.21 . Only one case (1%) had menarche at 11 years of age. 88% had menarche between 12-14 years and 11% between 15-18 years. All the cases in the study were married before 30 years of age. 13 % of the cases were married at ≤ 18 years, 37% between 19-21, 36% between 22-24 and 14 % between 25-30. The mean age at marriage was 21.59 ± 2.64 . Only one case

(1%) was nulliparous, 2% had one child, 41% had 2 children, 33% had 3 children and 23% had 4 children.

All the children were born before 30 years of age. All of the children have been breastfed.

Among the cases only 6% had used oral contraceptive pills but none had taken it for more than 6 months. 94% cases had never used oral contraceptive pills. 18% of the cases were pre-menopausal and 82% of the cases were post-menopausal. 11% cases attained menopause between 40-45 years of age, 67% between 46-50 and 4% after 50 years of age. None of cases had ever taken hormone replacement therapy.

None of the cases had been exposed to therapeutic radiation. Only one case (1%) had a first degree relative (mother) with breast cancer. None of the other cases had a first or second degree relative with breast cancer.

40% of the cases had none of the known risk factors for breast cancer. 42% cases had one risk factor, 15% had 2 risk factors and 3% had 3 risk factors (Table I). The summary of distribution of risk factors is seen in Table II.

DISCUSSION

Our study was conducted at Guru Nanak Dev Hospital, Amritsar. 100 Female patients with a diagnosis of breast cancer chosen for the study. 20% of the cases were illiterate and only 39% were educated up to matric or higher one of whom had completed post-graduation. 88% of the cases were housewives.

None of the cases in the study presented to the hospital at stage I of the disease. 53% were diagnosed at stage II and 45% were diagnosed at stage III. 2% cases had metastatic stage 4 disease at the time of presentation.

In our study, the youngest case was 32 years old and the oldest case was 85 years old. Mean age of presentation was 52.02 years with a standard deviation of 9.42 years. This finding is close to the mean age 50.1 with a standard deviation of 10.5 years found in a study done by Brinder Chopra et al. This age is much lesser compared to the United States of America where the mean age of presentation is 62 years.

In our study, mean BMI was 24.85 with a standard deviation of 2.98 with 40 percent of the cases had BMI above 25. A study by Tomi Akinyemiju et al had 43 % cases with BMI above 25.⁶

Mean age at menarche was 14.23 $\pm$ 1.21 years with only one case having menarche at 11 years and none earlier than that. In a study conducted in Mumbai by Dyavarishetty, 3.3% cases had their menarche before 12 years of age.⁷ In a study from Udipi, 31% cases had their menarche before 12 years of age.⁸ In a meta-analysis by collaborative group on hormonal factors in breast cancer, mean age at menarche was 13.1 years (SD 1.7) where 16% (49 464) of the controls reported menarche at age 11 years or younger.⁹

All the cases in our study were married. Only one case (1%) was nulliparous, 2% had one child and 97% cases were multiparous. In a study conducted in Mumbai by Dyavarishetty, 3% of the case were unmarried. 4.4% of the cases were had their first pregnancy after 30 years of age. In a study from Udipi, 56% of the cases had first pregnancy at 30 years or above. All the mothers had breastfed their child/children in our study. In the Mumbai study, only 1.6% did not breast feed their child.

6% of cases in our study had taken oral contraceptive pills but none of them had taken it for more than 6 months. In the Mumbai study, 2.8% cases had taken oral contraceptive pills. Similar finding was seen in the Udipi study.

18% of the cases in our study were pre-menopausal and 82 % were post-menopausal. Mean age at menopause was 46.82 $\pm$ 2.99 years. This age was lower than the mean age found in the meta-analysis by collaborative group on hormonal factors in breast cancer, in which mean age at natural menopause was 49.3 years (SD 4.6), with 15% (26 285 of 170 413) reporting menopause before age 45 years, 75% (127 984) between the ages 45 and 54 years, and 10% (16 144) at age 55 years or older. The RR of breast cancer increased by a factor of 1.029 (1.025–1.032, $p < 0.0001$) for every year older at menopause in the study. 4% of the cases in our study had attained menopause after 50 years of age.

In a study published in the New England Journal of Medicine, the relative risk of breast cancer among all current and recent users of hormonal contraception was 1.20 (95% confidence interval [CI], 1.14 to 1.26). This risk increased from 1.09 (95% CI, 0.96 to 1.23) with less than 1 year of use to 1.38 (95% CI, 1.26 to 1.51) with more than 10 years of use ($P = 0.002$).¹⁰ A more recent study in the JAMA Oncology found no association between Oral Contraceptive use and breast cancer.¹¹ In our study, 94 % of the cases had never taken any oral contraceptive pills. Only 6% of the cases had ever taken oral contraceptives at least once in their life time. None of the cases were taking oral contraceptive pills within 1 year of diagnosis of breast cancer and none of the cases had taken oral contraceptive pills for more than 6 months in their life time. In the Mumbai study, 2.8% cases had consumed oral

contraceptive pills and only 2 of them had consumed it for more than 5 years. A similar finding was seen in the Udipi study.

In a register-based cohort study in Norway, The hazard ratios associated with prescriptions of hormone replacement therapy for more than 1 year were 2.06 (1.90-2.24) for oestrogen + progesterone combinations and 1.03 (0.85-1.25) for systemic oestrogens. Invasive lobular carcinoma was more strongly associated with use of oestrogen and progesterone combinations, HR = 3.10 (2.51-3.81), than non-lobular carcinoma, HR = 1.94 (1.78-2.12).¹² In a study by Jones ME et. al, the hazard ratio in relation to current oestrogen plus progesterone hormone replacement therapy use relative to those with no previous use was 2.74 (95% confidence interval (CI): 2.05-3.65) for a median duration of 5.4 years of current use, reaching 3.27 (95% CI: 1.53-6.99) at 15+ years of use. The Hazard Ratio for oestrogen-only HRT was not increased (HR=1.00; 95% CI: 0.66-1.54).¹³ In our study, none of the patients had ever taken menopausal hormone replacement therapy.

In a study among patients of Hodgkin's Lymphoma who underwent chest radiotherapy, the pooled relative risk of secondary breast cancer was 8.23 (95% CI, 5.43-12.47, $I^2 = 96\%$). The relative risk was found inversely related to age at diagnosis of HL with the highest rate (68.7; [95 % CI, 28.08-168.11], $I^2 = 79\%$), occurred in young patients (≤ 15 years old), whereas the RR in older women ≥ 40 years old was not significant (0.55; [95% CI, 0.09-3.52]). Analysis of the effect of treatment modalities showed that the RR rates were (4.70; [95% CI, 3.28-6.75], $I^2 = 74\%$), (5.65; [95%CI, 2.94-10.88] for radiotherapy and radiotherapy + chemotherapy respectively.¹⁴ In our study, none of the cases had significant radiation exposure prior to their diagnosis.

Khazrami et al found that having family history of single (HR 1.8; 95 % CI 1.8-1.9) or multiple (HR 2.7; 95 % CI 2.6-2.9) relatives with breast cancer was associated with higher risk of breast cancer.¹⁵ In a study published in the JAMA Internal Medicine, first-degree family history was associated with an increased risk of breast cancer among women ages 65 to 74 years (hazard ratio [HR], 1.48; 95% CI, 1.35-1.61) and 75 years and older (HR, 1.44; 95% CI, 1.28-1.62).¹⁶ In our study, only one case which is 1%, diagnosed at 43 years of age, had a first degree relative, her mother, with breast cancer. None of the cases had any second-degree relative suffering from breast or ovarian cancer. In the Mumbai study, 0.7% of the cases had a positive family history. In the Udipi study, none of the cases had a positive family history. In a study in Kerala, 4.7% of the cases had a family history of breast cancer.¹⁷ Although only 1 case had a positive family history, 34% of the cases were diagnosed at < 50 years of age. Weitzel JN et al had found that patients diagnosed with breast or ovarian cancer at age < 50 years with a limited family history may have an underestimated probability of BRCA1/2 mutations based on family history alone.¹⁸

A meta-analysis by Key J et al that combined the results of 98 studies found excess risk associated with alcohol drinking was 22% (95% CI: 9-37%); each additional 10 g ethanol/day was associated with risk higher by 10% (95% CI: 5-15%).¹⁹ In our study only 4% cases, labourers by occupation, consumed alcohol. A comprehensive meta-analysis by Bagnardi V. et al found a relative risk of 1.61 for breast cancer with a clear dose- risk response.²⁰ Choi YJ et al found that

even very light (≤ 0.5 drink/day) drinking, led to an increased risk for breast cancer.²¹ 96% of the cases in our study denied ever having consumed alcohol.

A large EPIC cohort study found that when compared to women never exposed to smoking, current, former and currently exposed passive smokers were at increased risk of breast cancer (hazard ratios (HR) [95% confidence interval (CI)] 1.16 [1.05-1.28], 1.14 [1.04-1.25] and 1.10 [1.01-1.20]), respectively.²² In our study only 4% of the cases had a history of smoking. 96% of the cases had never consumed or smoked tobacco in any form. In the generations cohort study by Jone ME et al the hazard ratio (reference group was never smokers) was 1.14 (95% CI 1.03-1.25; $P=0.010$) for ever smokers, 1.24 (95% CI 1.08-1.43; $P=0.002$) for starting smoking at ages < 17 years, and 1.23 (1.07-1.41; $P=0.004$) for starting smoking 1-4 years after menarche.²³

In a meta-analysis of 139 prospective and retrospective studies by Hardefeldt PJ et al, physical activity significantly reduced the risk of breast cancer (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.76-0.81; $P < .001$), with high-intensity physical activity being slightly more protective (OR, 0.73; 95% CI, 0.65-0.81; $P < .001$) than low-intensity exercise (OR, 0.79; 95% CI, 0.72-0.86; $P < .001$). The effect size for general exercise was similar in both premenopausal (OR, 0.79; 95% CI, 0.73-0.87; $P < .001$) and postmenopausal (OR, 0.82; 95% CI, 0.78-0.86; $P < .001$) women. Additionally, weight loss reduced the risk of breast cancer incidence (OR, 0.82; 95% CI, 0.67-0.97).²⁴ In our study, Regular physical activity was undertaken by 78% of the cases. Only 22% cases did not undertake physical activity of some kind in their daily routine.

It was interesting to note that 40% of the cases in our study did not have any of the known risk factors for breast cancer and 60% had at least one risk factor for breast cancer. 16% of the women in the Mumbai study had at least one known risk factor for breast cancer. In the Udipi study, 79% cases had at least one risk factor for breast cancer.

Majority of the cases in our study had lifestyle related modifiable risk factors like high BMI and lack of physical activity. Other modifiable risk factors included smoking, alcohol and oral contraceptive pills. Only 7% of the cases had non modifiable risk factors which included family history and risk factors related to oestrogen exposure like early menarche, late menopause and nulliparity.

CONCLUSIONS

Hence, a large multi-centre study is needed to identify all known and possible risk factor of breast cancer relevant to the Indian population so that risk stratification can be used for earlier identification of patients with risk of breast cancer. This will help in earlier and more comprehensive treatment. This will be a stepping stone to the mammoth task of decreasing breast cancer mortality and morbidity which is currently the most common cancer in India.

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