



Socio-Demographic Factors and Their Associations with Receptor Subtypes: Observations from a South Indian Breast Cancer Patient Cohort

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Abstract

Introduction: Certain receptor subtypes of breast cancer are aggressive. Poor prognosis of these patients is often compounded by advanced stage at the time of diagnosis. An understanding of the relationship between risk factors associated with receptor subtypes and advanced-stage diagnosis would help in improving survival rates. In this study, we aimed to identify risk factors associated with different receptor subtypes and their relation with advanced-stage diagnosis.

Methods: A prospective cohort of 539 breast cancer patients visiting a private clinic in Bengaluru was used. Associations between variables for different breast cancer receptor subtypes and advanced-stage diagnosis and were derived by Odds Ratio (OR) by logistic regression and two-sided P-values <0.05 is considered significant.

Results: Symptomatic diagnosis (OR-3.5 (1.9-6.4)), lower education (OR-1.9 (1.3-2.8)) and lower economic condition (OR-3.1 (2.1-4.6)) were significantly associated with advanced-stage diagnosis. Patient's age at diagnosis >50 (OR-0.6 (0.42-0.87)), higher education (OR-1.64 (1.13-2.35)), upper economic standards (OR-1.68 (1.14-2.46)) and post-menopausal status (OR-0.64 (0.44-0.93)) were associated with HR+/HER2- disease. Pre-menopausal status (OR-1.47 (1.02-2.13)), lower education (OR-0.68 (0.47-0.98)) were associated with HER2+ disease. Age, ≤ 50 ((OR-1.7 (1.13-2.63)), lower economic status (OR-0.62 (0.40-0.95)) were associated with TNBC subtype. Symptomatic diagnosis among HR+/HER2-patients (P=0.0011), age below 50 years (P=0.02), lower education (P<0.0001) and lower economic status (P<0.0001) among HER2 + patients have shown to be risk factors for advanced-stage diagnosis in this cohort.

Conclusion: Dissemination of knowledge on risk factors and imparting education especially among patients of lower economic strata can improve early-stage diagnosis of breast cancer.

Keywords: Risk factors; Advanced-stage; Breast cancer; Receptor subtypes; Socio-demographic

Abbreviations

ER: Estrogen Receptor; PR: Progesterone Receptor; TNBC: Triple Negative Breast Cancer; HER2: Human Epidermal Growth Factor Receptor 2; OR: Odds Ratio; CI: Confidence Interval; SEER: Surveillance, Epidemiology and End Results; AJCC: American Joint Committee on Cancer

Introduction

Onset of breast cancer is influenced by various factors such as age, sex, reproductive, hormonal, pollution, radiation and hereditary, breast-related, lifestyle, socio-economic related factors [1,2]. Advanced-stage presentation is seen more frequently in developing countries than in developed countries and is the main reason for lower survival rates in these countries [3-5]. Breast cancer patients can have a good prognosis with effective treatment when diagnosed in the early-stage. The stage at which the disease is diagnosed is influenced by ethnicity, age at diagnosis, age of menarche, several modifiable factors like socio-economic condition, anthropometry, education, and age of the first child and duration of breast-feeding [6-13]. Receptor subtypes are also known to have specific associations with different races and socio-economic sub-groups [14,15].

No large cohort studies have been conducted on Asian patients and in particular Indian patients to understand the relationship between various risk factors and receptor subtypes, and thereafter

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stage at diagnosis in different receptor subtypes. Identifying the modifiable risk factors associated with late-stage diagnosis and subtypes will help in better management of breast cancer patients with improved quality of life. To our knowledge this is the first study where the interactions of various socio-economic factors, age, menopausal status, and reproductive factors have been investigated in the context of the stage of diagnosis and receptor subtypes, in a southern Indian patient cohort.

Methods

Ethics

This report is the analysis of the clinical data of patients who visited the hospital as part of their check-up/follow-up and as there was no intervention in the treatment of these patients, patient consent was not obtained for the study.

Study design

A total of 539 women were included in the study. Information on the date of birth, education, economic condition, height, weight, diet, menarche details, marital status and age at the first child were collected was collected by the treating clinician.

Patients diagnosed during a visit to a health care centre with a complaint were categorized as symptomatic diagnosis. Diagnosis during screening included patients who participated in the mobile mammogram, screening camps, and those who got tested due to awareness created by television/radio/newspaper/media.

The staging of the disease was as defined by AJCC. Stage I and II are categorized as early-stage and stage III and IV as the advanced-stage.

Subtype categorization: Patients positive either for ER or PR expression alone and negative for HER2 expression were considered as HR+/HER2- subtypes. Patients with HER2 overexpression irrespective of ER/PR expression are considered as HER2 positive

(HER2+) and patients with no expression of ER/PR/HER2 are considered as triple-negative patients (TNBCs).

The strength of association for sub-groups across variables tested here for different breast cancer subtypes and incidence of cancer in advanced-stages was obtained by Odds Ratio (OR) employing logistic regression and two-sided P-values across various groups were calculated by MedCalc. P-values <0.05 is considered significant.

Results

The study cohort had 53% of patients aged equal to and above 50 years. Eighty two percent of the cohorts were diagnosed symptomatically. Fifty seven percent of patients were overweight (BMI: 25 to 29) or obese (BMI: ≥ 30) and 53% were educated below 10th standard. Sixty one percent of patients were on a non-vegetarian diet and 63% of patients had enough financial resources to support surgery, radiation therapy, hormonal therapy and chemotherapy (Supplementary Table 1) [16].

Factors influencing advanced stage diagnosis

Almost half of the cohorts (45%) were diagnosed in advanced stages (Stage III and IV). Age at diagnosis, mode of diagnosis, education, financial status, obesity, menopausal status, dietary habits, and age at first child were analyzed for association with advanced-stage diagnosis of breast cancer patients. Patients diagnosed at ≤ 50 years, diagnosed symptomatically, who did not have enough financial resources and who were not educated beyond 10th standard had significantly higher diagnosis in advanced stage with a higher Odds Ratio (OR) (Table 1). Patients diagnosed symptomatically and patients with lower economic status were likely to have three times higher risk for advanced-stage diagnosis with an OR>3 (mode of diagnosis: 3.5 (95% CI, 1.9-6.4), affordability: 3.1 (95% CI, 2.1-4.6) (Table 1) over their respective counterparts. Patients aged ≤ 50 years at the diagnosis and those who were not well educated were likely to have 1.5 times (95% CI, 1-2.2) and 1.9 times (95% CI, 1.3-2.8)

Supplementary Table 1: Summary of age, the socio, economic demographics features of cohort.

| | Variables | Number of patients (%) |
|---|-----------------------------------|------------------------|
| | Total | 539 (100) |
| Age | ≤ 50 | 253 (47) |
| | >50 | 285 (53) |
| **Mode of diagnosis | symptomatic | 438 (82) |
| | Screening | 94 (18) |
| *BMI | Overweight (25-<30) +obese (≥ 30) | 233 (57) |
| | Normal (18.5-<25) | 159 (39) |
| | Underweight (<18.5) | 16 (4) |
| @Education | >10 th standard | 252 (47) |
| | <10 th standard | 286 (53) |
| Financial resources-Ability to self-fund for all kinds of treatment | Upper economic strata | 338 (63) |
| | Lower economic strata | 201 (37) |
| @Diet | Vegetarian | 209 (39) |
| | Non-vegetarian | 329 (61) |
| \$Age at first child | 20-30 yrs | 345 (72) |
| | <20 yrs | 128 (27) |
| Menopausal status | Pre-menopausal | 239 (44) |
| | Post-menopausal | 300 (56) |

*408, @538, **532, \$473

Table 1: Association with advanced stage diagnosis for various variables by Odds Ratio (OR).

| Variable | OR | 95% CI | P-value |
|-------------------------------------|------|-----------|---------|
| Less than 50/greater than 50 | 1.5 | 1-2.2 | 0.0198 |
| Less educated/more educated | 1.9 | 1.3-2.8 | 0.0003 |
| Lower economic/upper economic group | 3.1 | 2.1-4.6 | <0.0001 |
| Symptomatic/screening | 3.5 | 1.9-6.4 | 0.0001 |
| Pre-menopausal/post-menopausal | 0.98 | 0.6-1.4 | 0.9 |
| Age at first child 20-30/<20 | 0.7 | 0.4-1.1 | 0.16 |
| Normal weight/overweight + obese | 0.6 | 0.4-1 | 0.077 |
| Non-Vegetarian/vegetarian | 1.34 | 0.92-1.95 | 0.122 |

Table 2: Stage-wise distribution of patients across age groups.

| Age of the patient, years | Early stage (% of patients) | Advanced stage (% of patients) | P-value |
|---------------------------|-----------------------------|--------------------------------|---------|
| ≤ 40 | 43 | 57 | 0.006 |
| 41-50 | 53 | 47 | 0.0065 |
| 51-60 | 55 | 45 | 0.0014 |
| >60 | 70 | 30 | <0.0001 |

higher diagnosis in advanced-stage respectively, compared to their respective counterparts (Table 1). Patients who had their first child at age below 20 years (OR-0.7 (95% CI, 0.4-1.1)), those who were obese (BMI: ≥ 30) or overweight (BMI: 25-29) (OR-0.6 (95% CI, 0.4-1)) and those who had a non-vegetarian diet (OR-1.34 (95% CI, 0.92-1.95)) also presented with marginal risk for diagnosis in advance stage (Table 1). Pre- and post-menopausal women were likely to have a similar risk of diagnosis in an advanced stage with an OR of 0.98 (95% CI, 0.6-1.4) (Table 1).

Age at diagnosis and stage at diagnosis were inversely correlated. With increase in age, the number of patients diagnosed in advanced stage decreased significantly (Table 2).

Correlation of age at diagnosis with receptor subtypes

The cohort had significantly higher proportions of HR+/HER2- (39%) and HER2+ (38%) over TNBCs (23%) (P<0.0001) [16].

Diagnosis with TNBC disease in young patients was higher with an OR of 1.7 (95% CI, 1.13-2.63). However, this was reverse in HR+/HER2- patients with an OR of 0.6 (95% CI, 0.42-0.87) (Table 3), while HER2+ disease do not seem to be associated with age with an OR of 1 (95% CI, 0.36-1.53) (Table 3).

HR/HER2- (early-stage, 60%; advanced-stage- 40%) and TNBC (early-stage, 62%; advanced-stage- 38%) had diagnosis more in early-

stages compared to HER2+ patients (early-stage, 43%; advanced-stage- 57%) [16]. On exploratory analyses, both HR+/HER2- and TNBC subtypes had no significant differences in early and advanced/late-stage diagnosis (P=0.2 and 0.5) in younger patients (≤ 50), however early-stage diagnosis was significantly higher (P<0.0001) in older patients (>50) in these two receptor subtypes (Table 4).

Interestingly, HER2+ disease showed an inverse representation of HR+/HER2- and TNBC disease. In younger patients, advanced-stage diagnosis (early-stage, 41%; advanced stage, 59%; P=0.02) was higher and the older patient group had similar proportions of patients diagnosed in early and advanced stages (P=0.7).

Association of screening programs with receptor subtypes

In general, fewer women participated in screening programs (18%) (Supplementary Table 1) [16]. All three subtypes (HR+/HER2, HER2+, TNBC) were similarly diagnosed by both the diagnostic methods; symptomatic and screening (Table 3).

As early-stage diagnosis was higher in HR+/HER- and TNBC patients, it was also so by both modes of diagnosis, screening and symptomatic (Table 4). Early-stage patients were significantly higher (P<0.05) in both these receptor subtypes by both modes of diagnosis (Table 4). In HER2+ patients there were no significant differences across both the stages in both modes of diagnosis (Table 4).

Association of socio-economic factors with receptor subtypes

HR+/HER2- disease was associated with women who good education and economic standards with an OR of 1.64 (95% CI, 1.13-2.35) and 1.68 (95% CI, 1.14-2.46) respectively (Table 3). HER2+ was seen more often in women did not receive education beyond 10th standard with an OR of 0.68 (95% CI, 0.47-0.98) and TNBC in women with lower economic standards with an OR of 0.63 (95% CI, 0.4-0.95) (Table 3).

As observed in total cohort even in sub-groups of lower and higher education early-stage diagnosis was higher in women with HR+/HER2- and TNBC disease (Table 4). The early and advanced stage patient distributions did not coincide with total cohort in women with HER2+ disease. In women with lower education standards advanced stage diagnosis was significantly higher (P<0.0001), however in women with higher education early-stage diagnosis was higher (P=0.0007) in this receptor subtype (Table 4).

Similarly, early-stage diagnosis was significantly higher in women with good economic standards with HR+/HER2- and TNBC receptor

Table 3: Association of receptor subtypes with various variables by odds ratio. CI: Confidence Interval.

| Variable | HR+/HER2- | | | HER2+ | | | TNBC | | |
|---|-----------|-----------|---------|-------|-----------|---------|------|-----------|---------|
| | OR | 95% CI | P-value | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Age: ≤ 50/>50 | 0.6 | 0.42-0.87 | 0.007 | 1 | 0.36-1.53 | 0.61 | 1.7 | 1.13-2.63 | 0.01 |
| Mode of diagnosis: Screening/symptomatic | 1.4 | 0.8-2.4 | 0.19 | 0.6 | 0.33-1.08 | 0.08 | 1.15 | 0.6-2.1 | 0.64 |
| Education: Beyond 10 th standard/below 10 th standard | 1.64 | 1.13-2.35 | 0.007 | 0.68 | 0.47-0.98 | 0.04 | 0.76 | 0.5-1.15 | 0.2 |
| Economic status: upper/lower | 1.68 | 1.14-2.46 | 0.0075 | 0.85 | 0.58-1.24 | 0.4 | 0.62 | 0.40-0.95 | 0.02 |
| Pre-menopausal/post- menopausal | 0.64 | 0.44-0.93 | 0.019 | 1.47 | 1.02-2.13 | 0.03 | 1.07 | 0.7-1.64 | 0.72 |
| Age at first child: 21-30/<20 | 1.24 | 0.8-1.9 | 0.32 | 0.81 | 0.52-1.25 | 0.34 | 0.98 | 0.59-1.6 | 0.9 |
| BMI: Normal weight/Obese + Over weight | 1.2 | 0.78-1.83 | 0.39 | 0.84 | 0.54-1.3 | 0.45 | 0.96 | 0.59-1.57 | 0.89 |
| Diet: Vegetarian/Non-vegetarian | 1.4 | 0.97-2 | 0.06 | 0.8 | 0.55-1.18 | 0.26 | 0.82 | 0.53-1.27 | 0.38 |

Table 4: Distribution of early and advanced stage patients across sub-groups of all variables.

| Variable | subgroups | Cancer stage [Early stage (ES), Advanced stage (AS)] | Hormone receptor positive/HER2 negative (% of patients) | P-value between early and advanced stages within a subgroup | HER2 positive (% of patients) | P-value between early and advanced stages within a subgroup | TNBC (% of patients) | P-value between early and advanced stages within a subgroup |
|---------------------------------|---------------------------------|--|---|---|-------------------------------|---|----------------------|---|
| Age of the patient at diagnosis | ≤ 50 | ES | 55 | 0.2 | 41 | 0.02 | 53 | 0.5 |
| | | AS | 45 | | 59 | | 47 | |
| | >50 | ES | 68 | <0.0001 | 49 | 0.7 | 76 | <0.0001 |
| | | AS | 32 | | 51 | | 24 | |
| Mode of screening | Screening | ES | 95 | <0.0001 | 44 | 0.07 | 75 | 0.0029 |
| | | AS | 5 | | 56 | | 25 | |
| | symptomatic | ES | 59 | 0.0016 | 45 | 0.5 | 61 | 0.0005 |
| | | AS | 41 | | 55 | | 39 | |
| Education | Below 10 th standard | ES | 59 | 0.0145 | 34 | <0.0001 | 63 | 0.0049 |
| | | AS | 41 | | 66 | | 37 | |
| | Above 10 th standard | ES | 66 | <0.0001 | 60 | 0.0007 | 63 | 0.0104 |
| | | AS | 34 | | 40 | | 37 | |
| Financial resources | Good economic standards | ES | 68 | <0.0001 | 59 | 0.909 | 73 | <0.0001 |
| | | AS | 34 | | 41 | | 27 | |
| | Lower economic standards | ES | 53 | 0.5 | 23 | <0.0001 | 50 | 1 |
| | | AS | 47 | | 77 | | 50 | |

subtype ($P < 0.0001$), whereas there were no differences across the stages in lower economic groups in these two-receptor subtypes (Table 4). Advanced-stage diagnosis was significantly ($P < 0.0001$) higher in sub-group with lower economic standards in women with HER2+ disease with no differences in women with higher economic standards in this receptor subtype (Table 4).

Association of menstrual, reproductive factors and body weight with receptor subtype diagnosis

Pre-menopausal women showed higher association with HER2+ (42%) with an OR of 1.47 (95% CI, 1.02-2.13) (Table 3), whereas post-menopausal women were associated with HR+/HER2-disease with an OR of 0.64 (95% CI, 0.44-0.93) (Table 3).

Although TNBC patients showed higher association with patients below 50 age group, stratification by menopausal status did not reveal any differences in their proportions across the pre- and post-menopausal sub-groups with an OR of 1 (95% CI, 0.7-1.64) (Table 3).

Childbearing age, body mass index and diet of the patient did not have any association with any subtype (Table 3).

Discussion

The stage at diagnosis plays a crucial role in the prognosis of the patient and is the deciding factor on the treatment strategy. Global statistics have shown that early-stage patients have overall good prognosis compared to patients diagnosed in late-stages. Multiple studies have shown that 5-year breast cancer-specific survival rates have ranged from 90% to 97% for stage I, 87.8% to 89% for stage II and 51% to 73% for stage III and overall survival rates were: Stage I up to 99%, stage II up to 90%, stage III up to 27% and stage IV 10% [17-23].

Early-stage diagnosis is well achieved in developed countries. In developing countries this remains a challenge. Differences among races/ethnicities in incidence, survival outcomes, and receptor subtypes of US breast cancer patient data point to a need for

identification of underlying risk factors associated with incidence and diagnosis of each cohort for implementation of effective treatment plans [23]. Towards this goal, we have investigated associations of various factors like age, socio-economic, menstrual and reproductive factors with different receptor subtypes and stage of the disease at diagnosis in the present South Indian patient cohort.

Age has been one of the important risk factors for breast cancer and changes in lifestyles has reduced the median age of diagnosis across all the races and more so among Indian breast cancer patients [24-28]. Our study corroborates with earlier findings that younger patients present with late-stage and the proportions of early-stage diagnosis increases with increase in age at the time of diagnosis [7,29]. This could partly be due to lower participation of younger women, below 40 years, in the screening programs. Only 9% of the patients diagnosed by screening were below 40. Breast cancer screening has been consistently associated with early-stage detection of breast cancer, both in clinical trials and in regular clinical practice [30-37].

We found that lower education and lower economic status were associated with late-stage diagnosis. Both of these social factors are interlinked. Lack of higher education is one of the most important causes of delay in referring to clinicians about disease symptoms and influences lifestyle, economic status, marital status and parity [8,13,38,39]. Interestingly this association of advanced-stage diagnosis with lower economic status is similar both in developed and developing countries [9,10,12,29,36,38,40].

In our study higher education, economic status, age above 50, and post-menopausal status were all associated with HR+/HER2-receptor subtype, this observation is in line with other studies [41]. Since older patients, typically aged above 40, participate in screening programs and as the disease was more common in older patients, it is obvious that many of the patients diagnosed by screening would be HR+/HER2-. In the present study, half of the patient sub-group diagnosed by screening was HR+/HER2-. Association of HR+/HER2-

patients with high levels of education and economic status is likely to have further increased participation in the screening programs. Considering the lower diagnosis by screening (18%), increased diagnosis by screening methods is required across both age groups, particularly in patients aged less than 50 years in order to decrease late-stage diagnosis among HR+/HER2- patients. This should be facilitated and encouraged both by government and private bodies in order to achieve early-stage diagnosis of HR+/HER2- patients.

HER2+ receptor subtype patients were associated with lower economic condition and premenopausal status, in the current study cohort. There are conflicting reports on association of HER2+ subtype with menopausal status [41]. A HER2+ disease typically have aggressive biology, tend to grow faster and are known to have poor prognosis [42]. As lower education and lower economic conditions were significantly associated with advanced stage, current findings suggest that these two are risk factors for late-stage diagnosis of this receptor subtype.

We observed that TNBCs were mostly patients below 50 years and had lower economic status. Similar observations were made in other cohorts across different races that TNBC [14,15,24]. Free screening campaigns will diagnosis in young patients.

Thus, the study identifies key socio-economic factors associated with different receptor subtypes of breast cancer. We understand that the cohort size is the limitation of the study. Large cohort observations are required to substantiate these findings.

Conclusion

In summary, our study identified many factors responsible for advanced-stage diagnosis. Routine screening and increase in awareness of breast cancer risk factors among all the strata of society is required. The findings of this study require quick attention and implementation of suitable policies to increase the early-stage diagnosis of breast cancer patients.

Author Contributions

JT guarantees the integrity of the entire study. JT and MN collected the data. AG analyzed the data and drafted the manuscript. AG, JT, MB reviewed the manuscript. All authors have read and approved the final manuscript.

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