



Survival Probability and Prognostic Factors: A Tertiary Care Hospital-Based Study on Female Breast Cancer Patients in South India

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Abstract

Introduction: Breast cancer is the leading cause of cancer death in women across the globe and is the most common cancer among Indian women. Survival studies are a benchmark to formulate cancer control strategies. However, only a few survival studies focus on the contexts in developing countries.

Aims and Objectives: To estimate the survival of breast cancer cases registered in Government Royapettah Hospital Chennai during 2007-2014. To assess the various prognostic factors (age at diagnosis, stage of diagnosis, and clinical extent of the disease) affecting the survival of breast cancer.

Methods: The paper draws insights from a retrospective study of 744 cases registered and treated between January 2007 and December 2014 in the South Indian city of Chennai. The inclusion criteria of the study were all female breast cancer cases. In contrast, the exclusion criteria for the study were the data missing variables such as age at diagnosis, size of the tumour, type of tumour, and stage of the tumour in the female breast cancer medical records. Breast cancer cases with secondary malignancies cases are excluded. The database contains information on demographic factors, clinic-pathological features of the tumour, and therapeutic factors. This study analyses the pattern of breast cancer survival rate and assesses various prognostic factors that affect the survival of breast cancer among females.

Results: The overall five-year survival was 68%. The incidence of breast carcinoma is high in postmenopausal women. The survival of breast cancer was significantly associated with the stage of the tumour.

Conclusion: This study recommended opportunistic breast cancer screening in public health care facilities and should strengthen the referral process to increase the survival by early treatment of breast cancer patients.

Keywords: Breast Cancer; Survival, Prognostic Factors; Cox-Proportional Hazard; Kaplan-Meier Model; India

Key Messages

Cancer studies measure the length of survival after cancer diagnosis and treatment. Survival data are not readily available in many developing countries because of inadequate information systems to collect reliable data on the mortality of cancer patients. This study feeds into ongoing research and policy discussions on the survival of breast cancer patients. Considering the large number of cases (32%) reported in women between 40-49 years of age, focused screening among this age group may improve early detection and survival.

Introduction

Globally, cancer is the second leading cause of death after cardiovascular disease [1]. Breast cancer is now the leading cause of global cancer, accounting for 11.7% of the 2.3 million new cancer cases [2]. According to recent estimates of the worldwide cancer burden, around 18.1 million new cases and 9.6 million deaths reported in 2018 were due to cancer (WHO Press release: 12 Sep-

tember 2018). The global disease burden suggests that about 70% of all cancer deaths are now concentrated among low and middle-income countries [3]. Compared with patients in high-income countries, factors such as relatively low cancer awareness, late diagnosis, and lack of or inequitable access to affordable, curative services have contributed to this trend [4]. Cancer cases related to lung, female breast, and colo-rectum were found to be the three most common types in terms of incidence and mortality; they constitute nearly one-third of the cancer burden reported worldwide [5]. Breast cancer is the most common type of cancer in women and the second most common after lung cancer [6].

In India, According to the Globocan Statistics 2020, BC contributed to 13.5% (178361) of all cancer cases and 10.6% (90408) of all fatalities in India, with a cumulative risk of 2.81 [7]. In terms of the total cancer burden in India, the International Agency for Research in Cancer (IARC) in Lyon (GLOBOCAN project) predicts that breast cancer incidence in India will rise from one million cases in

2012 to nearly 1.7 million in the next 15 years [8]. The National Cancer Registry Programme (NCRP) predicts that almost 2,30,000 breast cancer cases will be recorded yearly by 2025, with a consistent increase in the incidence of breast cancer among young women (45 years of age) [9,10].

One in every fifty Indian women develops cervical cancer, and only one in two women survives five years after breast cancer diagnosis. The evidence also indicates a higher proportional prevalence in younger age groups than the global average [11]. Breast cancer is the most common cancer among urban Indian women and the second commonest among rural women [12]. Female breast cancer, male lung cancer, and oesophageal cancer contributed the most burdens in the country. In addition to considerable morbidity and mortality, these cancers are emerging as a significant cause of suffering and impoverishment across the country [13].

In India, the highest crude DALY rates for breast cancer were in Kerala, Punjab, and Tamil Nadu. The highest incidence is in Chennai at 42.2 per lakh [9]. Breast cancer is the most common cancer reported among women in Chennai; it accounts for 30.7% of all cancers reported in women in Chennai. Breast cancer is more common in the younger age group; nearly 49% of all women with breast cancer in Chennai are below 50. In 1982-1983, breast cancer accounted for 20% of all cancers reported among women in Chennai, which increased to 27% by 2012 [1].

Globally, the survival rate varies across the countries. High-income countries such as the United Kingdom, Canada, Australia, Northern Europe, and Western Europe are predicted to have 5-year survival rates of more than 85%. In comparison to low- and middle-income nations such as South Africa (53%), Algeria (38.8%), and Brazil (58.4%), the United States has a 5-year survival rate of 83.9%. In India, the corresponding figure is not more than 60%. Several factors, including a lack of awareness of breast cancer and delays in screening, contribute to such differences. The Western nations are steadily improving and achieving good survival, mainly because of screening for breast cancer. Mammography screening recommendations are not available in most underdeveloped countries [14].

Cancer studies generally measure the length of survival after cancer diagnosis and treatment [15]. Survival data are not readily available in many developing countries because of inadequate information systems to collect reliable data on the mortality of cancer patients. Not all cancer patients die of cancer; as age advances, cancer patients die more of causes other than cancer. Survival of breast cancer is defined as 'the duration from the date of diagnosis of breast cancer until either death from any cause or date last known to be alive for patients who are not known to have died [16]. A patient who dies of breast cancer during the study period can be considered to have an 'event' at their date of death. The patient may die due to causes unrelated to the disease; such events are termed "competing risk events". Survival at a given time is 'the conditional

probability of surviving to a specific time given that the individual is at risk for the event (such as mortality) at that time' [17].

Breast cancer patients' chances of disease-free survival have increased over the last few decades; however, this applies only if the disease is diagnosed early and is limited to the primary organ site. Breast cancer does not strike individuals alone but the whole family unit. Therefore, the impact of breast cancer is profound on both the women diagnosed with the disease and their families. Their fear and anxiety over the eventual outcome of illness may manifest themselves through behavioural changes. From the perspective of public health management, these factors underline the importance of personal and social experience while addressing the challenges faced by the patients and the families extending the care.

Aims and Objectives

- To estimate the survival of breast cancer cases registered in Government Royapettah Hospital Chennai during 2007-2014.
- To assess the various prognostic factors (age at diagnosis, stage of diagnosis, and clinical extent of the disease) affecting the survival of breast cancer.

Material and Methods

The study is based on the data collected from the medical records of the Government of Royapettah Hospital Chennai on female breast cancer cases registered from 2007 to 2014. From 918 female breast cancer registered during this period, relevant information was unavailable for 174 cases. Thus, the final sample covered 744 cases of female breast cancer. The medical records of breast cancer patients provided the patient's status (event-death) for 83 cases. The morbidity data has been complemented with primary data collected by reviewing the medical records and cases under active follow-up. The researcher also attempted to track the present status of the patients through direct interviews during their follow-up visits at the hospital (12 cases). Due to the outbreak of the COVID-19 pandemic and lockdown restrictions, the researcher had to discontinue this process. The researcher tried to track the present status of 485 patients (contact number was unavailable for 259 cases) through telephonic interviews. Even with multiple attempts, the current situation was updated for 174 cases, while there was no response (or could not connect to the given number) for the remaining 216 cases.

The database contains information on demographic characteristics (registration date, age, geographical origin, occupation, age at menarche, age at menopause, and parity), clinico-pathological features of the tumour (size of the tumour, type of tumour, number of nodes, and stage of tumour), therapeutic factors (like neo-adjuvant chemotherapy, adjuvant chemotherapy, radiotherapy, surgery and type of surgery), the status of the patient and last follow up. The inclusion criterion for the study was histopathologically proven breast cancer diagnosed between January 2007 and December 2014. The clinical data were collected from patient medical records. The exclusion criteria for the study were the data missing

for more than four variables (stage of the tumour, type of tumour, size of the tumour, and age at diagnosis) in the medical records, and breast cancer cases with secondary malignancies were excluded. The last date of follow-up was 29 February 2020. This study has examined the survival experience over five years in breast cancer patients treated at Government Royapettah Hospital Chennai from 2007 to 2014. The study followed the Kaplan-Meier method and the Cox-Proportional Hazard Model for analyzing survival data with different prognostic factors (age, stage of diagnosis, and clinical extent of the disease).

Ethical consideration

This study was approved by the Scientific Research Committee and Ethical Committees constituted by The Tamil Nadu Dr. M.G.R. Medical University, Chennai (Project No: ECMGR0309119). Informed consent was obtained from all individual participants included in the study.

Statistical analysis

All analyses used Statistical Package for Social Sciences (SPSS) software Version 21.0 (Armonk, NY: IBM Corp). All the variables are categorized into two groups: socio-demographic factors and clinic-pathological factors. Each model included all the variables from the particular group. Studies follow different methods while analyzing the data sets with missing variables to ensure better results and transparency of research findings. A recent study reviews different methods for analyzing data sets with missing variables. Based on this, the present study follows the 'Cox proportional hazard' model that involves replicating the original data set multiple times and, in each replication, replacing the missing values with plausible observations [17]. The survival time was estimated using the Kaplan-Meier method, while the Cox regression method was adopted to estimate the proportional hazard with different prognostic factors.

Results

Socio-demographic variables	Censored n (%)*	Died No. n(%)*	Total No. n(%)*	Chi-square	p-value
Age at diagnosis (739 cases); years				5.167	0.023**
≤50	369 (49.9%)	90 (12.2%)	459 (62.1%)		
>50	205 (27.7%)	75 (10.2%)	280 (37.9%)		
Menarche age (644 cases); years				0.042	0.837
≤13	206 (32.0%)	57 (8.8%)	263 (40.8%)		
>13	301 (46.8%)	80 (12.4%)	381 (59.2%)		
Menopausal status (709 cases)				0.385	0.535
Pre menopause	270(38.1%)	73 (10.3%)	343 (48.4%)		
Post menopause	281 (39.6%)	85 (12%)	366 (51.6%)		
Parity (676 cases)				0.97	0.756
Nulli Para	70 (10.4%)	19 (2.8%)	89 (13.2%)		
Multi Para	453 (67%)	134 (19.8%)	587 (86.8%)		

Table 1: Effect of Sociodemographic Variables on Survival Among Women Diagnosed With Breast Cancer.

** Statistically significant; * Row- wise percentage.

Table 1 shows the distribution of social-demographic factors of breast cancer patients. The distribution of cases according to the age at diagnosis reveals that most subjects were censored in 574 (77.6%) and events occurred in 165 (22.4%) cases. The mean age at diagnosis was 48 years. The distribution of cases according to the age at menarche shows that 381 cases (59.2%) of patients attained menarche above 13 years. Most subjects were censored 507 (78.8%), and events occurred in 137 (21.2%) women. The maximum number of censored and death cases attained menarche above 13 years. The mean age at menarche was 13 years. The distribution of cases according to menopausal status data shows that most patients, 551 (77.7%), were censored, and events occurred in 158 (22.3%) of cases. This table shows a slight preponderance of breast cancer in postmenopausal women 366 (51.6%) compared to premenopausal women 343 (48.4%). The majority of the censored and death cases occurred in postmenopausal women. The

distribution of patients according to the parity, the table shows that in most cases 551 (77.4%) were censored, and events occurred in 158 (22.3%) of cases. Overall, the present study finds that most breast cancer patients, 587 (86.8%), are multiparous, and only 89 breast cancer patients (13.2%) are Nulliparous. The majority of the censored and death cases occurred in multiparous women. The unifactorial analysis of socio-demographic factors' association with survival suggests that only age at diagnosis is significantly associated with survival (p-value -0.023).

Table 2 presents the distribution of clinicopathological variables of women with breast cancer. The unifactorial analysis finds that greater tumour size, positive axillary lymph nodes, clinical classifications of the tumour, and metastasis at the time of diagnosis were significantly associated with poor survival. About 525 cases (77%) of women were reported with tumour sizes above

Clinicopathological variables	Censored n (%) [*]	Died n (%) [*]	Total n (%) [*]	Chi-square	p-value
Tumour size (682 cases)				14.899	0.001**
<2cm	20 (2.9%)	3 (0.5%)	23 (3.4%)		
2-5cm	120 (17.5%)	14 (2.1%)	134(19.6%)		
>5cm	392 (57.5%)	133(19.5%)	525 (77%)		
Type of Tumour (711 cases)				4.822	0.090
Invasive breast cancer	512 (72%)	138(19.4%)	650(91.4%)		
Non-invasive breast cancer	27 (3.8%)	15 (2.1%)	42 (5.9%)		
Mixed connective and epithelial cancer	15 (2.1%)	4 (0.6%)	19 (2.7%)		
No. of involved lymph nodes (716 cases)				16.985	≤0.001**
Node negative	181 (25.3%)	26 (3.6%)	207(28.9%)		
1-3 positive node	371 (51.8%)	133(18.6%)	504(70.4%)		
4 and above 4 positive node	3 (0.4%)	2 (0.3%)	5 (0.7%)		
Clinical classification (718 cases)				9.668	0.008**
EBC	299 (41.6%)	67 (9.4%)	366 (51%)		
LABC	127 (17.7%)	43 (6%)	170(23.7%)		
MBC	128 (17.8%)	54 (7.5%)	182(25.3%)		

Table 2: Effect of Clinico-Pathological Variables on Survival Among Women Diagnosed With Breast Cancer.

**-Statistically significant, EBC-Early breast cancer, LABC-Locally advanced breast cancer, MBC-Metastatic breast cancer;

* Row-wise percentage.

5cm, and 23 cases (3.4%) were reported as tumour sizes less than 2cm. The event happened for 133(19.5%) women with a 5cm tumour size and 3 (0.5%) women with less than 2cm tumour size. About 504 (70.4%) of women were reported with 1-3 positive axillary lymph nodes, and 207(28.9%) were reported as node-negative cases. There was a rise in death 133 cases (18.6%) in those women

with 1-3 positive axillary lymph nodes compared to 26 (3.6%) node-negative patients.

Kaplan-Meier analysis of survival time among women diagnosed with breast cancer

Factor	Survival time (years) Mean ± SE (95%CI)	Log-rank test (p-value)
Age at diagnosis		≤0.001**
≤50 years	9.2 ± 0.3(8.5-9.8)	
>50 years	7.7 ± 0.4(6.8-8.5)	
Menopausal status		0.52
Premenopause	8.5 ± 0.35(7.8-9.2)	
Post menopause	8.6 ± 0.34(7.9-9.3)	
Parity		0.304
Nullipara	9.1 ± 0.65(7.7-10.3)	
Multi para	8.4 ± 0.27(7.9-8.9)	
Tumour size		≤0.001**
<2cm	8.7 ± 0.75(7.3-10.2)	
2-5cm	10.7 ± 0.42(9.8-11.5)	
>5cm	8.8 ± 0.23(7.5-8.7)	
Types of tumour		0.137
Invasive breast cancer	8.7 ± 0.27(8.2-9.3)	
Non-invasive breast cancer	5.7 ± 0.68(4.4-7.1)	
Mixed connective and epithelial cancer	8.3 ± 1.2(6-10.6)	
Pathological axillary lymph node		≤0.001**
Node negative	10 ± 0.36(9.3-10.8)	
1-3 positive node	7.9 ± 0.31(7.3-8.5)	
4 and above 4 positive node	2.9 ± 1.2(0.53-5.2)	

Clinical classification of tumour		≤0.001**
EBC	9.3 ± 0.33(8.6-9.9)	
LABC	8.6 ± 0.5(7.6-9.5)	
MBC	6.5 ± 0.48(5.6-7.5)	

Table 3: Kaplan-Meier Analysis of Survival Time Among Women Diagnosed With Breast Cancer.

**-Statistically significant, EBC-Early breast cancer, LABC-Locally advanced breast cancer, MBC-Metastatic breast cancer.

The Kaplan-Meier analysis shows the mean survival times, standard error, and 95% confidence interval for a different group with a log-rank test for comparing the survival time for other groups. The patient’s overall survival (OS) was calculated as the interval between the registration date and the last follow-up. The data closure date was taken as 29 February 2020. By the end of the follow-up (29 February 2020), 576 (77.4%) cases were censored, and 168 (22.6%) patients had an event (death). Table 3 shows a significant difference between different groups in age at diagnosis, tumour size, pathological axillary lymph node, and clinical tumour classification. The mean survival time was 8.6 ± 0.25years, and the 95% CI was 8.1-9.1.

Survival according to clinical classification of breast cancer

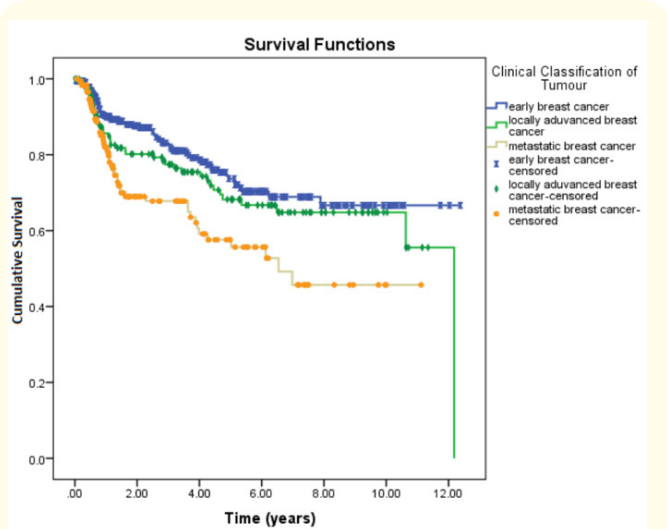


Figure 1: Kaplan-Meier curves of overall survival and clinical classification. (Source: Primary data collected by authors).

Figure 1 presents the survival probability of breast cancer according to the clinical classification of the tumour. Patients with early breast cancer had the highest 5-year survival rate of 70.3% than those with locally advanced and metastatic breast cancer (68.2% and 57.6%, respectively). Thus, higher stages were found to have a poorer prognosis than lower stages.

Table 4 presents the overall survival probability among breast cancer patients with the number of people at risk concerning time (In years). Of 744 cases, 181(68.7%) women were in the risk group at five years, 122 (66.3%) women were at risk at more than five years, and 160 women died at the end of 5 years. The overall 5-year survival probability among women with breast cancer was estimated as 68.7 percent, and the overall survival probability at more than five years was 66.3 percent. The table shows that the survival probability was decreasing with the increase of time.

Multifactorial analysis of socio-demographic and clinic-pathological variables

Table 5 presents the Cox proportional hazard regression analysis for determining independent prognostic factors for overall survival. All the elements that were found to influence overall survival in univariate analysis, such as age at diagnosis, menopausal status, parity, tumour size, type of tumour, and pathological axillary lymph node, were considered for further multivariate analysis. Thus, using Cox proportional step-down reduction method, we found that higher age at diagnosis, i.e., above 50 years (HR = 1.7, 95% CL = 1.5, 2.2, P ≤ 0.001), invasive breast cancer (HR = 7.4, 95% CL = 3.1, 33.5, P = 0.014), and tumour with positive axillary lymph node (HR = 1.5, 95% CL = 1.3, 2.0, P ≤ 0.001) are independent predictors for poor overall survival in breast cancer patients. The hazard ratio for invasive breast cancer was seven times higher than for non-invasive breast cancer (marginally significant). The hazard ratio for post-

Table 4: Overall Survival Probability Among Women With Breast Cancer.

Time (in years)	Number at risk	Censored	Event	Survival probability (%)
0	744	183	82	87
1	479	88	28	86.8
2	363	45	14	81.4
3	304	49	16	78
4	239	44	14	73.5
5	181	53	6	68.7
>5	122	114	8	66.3

Parameter	Univariate		Multivariate	
	HR (95%CL)	p-value	aHR (95% CL)	p-value
Age at diagnosis				
≤50 years	1		1	
>50 years	1.6 (1.4,2.2)	0.004**	1.7 (1.5,2.2)	0.001**
Menopausal status				
Pre-Menopause	1			
Post-Menopause	3.3 (2.1,6.9)	0.048**	-	-
Parity				
Nulli Para	1			
multi Para	2.1 (1.5,3.8)	0.34	-	-
Tumour Size				
<2cm	1		-	-
≥2cm	1.3 (1.0, 6.8.)	0.19		
Type of Tumour				
Non-invasive breast cancer	1		1	
Invasive breast cancer	7.5 (3.2,33.6)	0.014**	7.4 (3.1,33.5)	0.014**
Pathological axillary lymph node				
Node negative	1		1	
Node positive	1.6 (1.3,2.1)	0.001**	1.5 (1.3,2.0)	0.001**

Table 5: Factors association on the overall survival using Cox proportional hazard regression.

§ Abbreviations: HR, hazard ratio; CL, confidence limit, ** Significant (p-value <0.05)

aHR (95% CI): adjusted Hazard Ratio (95% confidence limit).

menopausal women was three times higher than for premenopausal women (marginally significant). The risk of multiparous women was twice as high as that of nulliparous women (not statistically significant).

Discussion

Cancer studies are the benchmark to formulate cancer control strategies. Age, menopausal status, and clinical extent of the disease are the significant prognostic factors for breast cancer survival. Age at diagnosis was the critical prognostic factor affecting breast cancer survival. The present study finds the maximum number of breast cancer cases diagnosed at ≤ 50 years. This trend also follows a similar pattern in some earlier studies in the Indian context [2, 9, 10, 19]. The present study finds that the mean age at diagnosis was 48 years, and most cases were reported at less than or equal to 50 years. A similar pattern was identified in some other studies in the international context. While in most of the developed countries, the majority of breast cancer cases were reported in 60-70 years [11, 20].

The present study's findings confirm that early menarche was not a risk factor for breast cancer, as highlighted in some existing studies [16]. The present study shows a slight preponderance of breast cancer in postmenopausal women (52%) compared to premenopausal women (48%). Some studies show that late-age menopause has increased the risk of developing breast cancer [11]. Some studies showed that nulliparous women had an increased

risk of developing breast cancer [21]. However, the result of the present study did not find nulliparous women to be a risk factor for breast cancer. As the study is based on a hospital-based registry, most women were multiparous (86.8%). Broadly, 60-70% of cases in developed countries were reported in the early breast cancer stage [20]. Compared to this, the present study finds that 51% of patients are in the early breast cancer stage.

The present study also confirms the significant association between the years' overall survival rate of breast cancer patients and the size of the primary tumour. Patients with a tumour size of more than 5 cm had a poorer prognosis than patients with smaller-sized tumours. This difference was found to be statistically significant (p = 0.001). The study found that patients with tumour sizes of 5cm and above died more than the patients with less tumour size. These results are consistent with some existing studies [11]. The result of clinical factors indicates that most respondents (70.4%) were presented with 1-3 positive axillary lymph nodes. The present study demonstrates that greater tumour size, tumour stage, and the number of involved lymph nodes were significantly associated with poor survival. This study finds that positive axillary lymph nodes increased breast cancer-related death. These results are consistent with some existing studies [11].

The present study estimated the five-year overall survival of early breast cancer, locally advanced breast cancer, and metastatic breast cancer as 70%, 68%, and 57%, respectively, and suggests

that late-stage presentation has a poorer prognosis [22,23]. The study also estimated the overall survival of breast cancer at 1, 3, and 5 years as 87%, 78%, and 68.7% respectively. A similar pattern was shown in some of the existing studies [24]. This study finds that the overall five-year survival of breast cancer was 68.7 percent, which was higher than in Uganda (44%), Malaysia (49%), and Iran (62%) and lower than that of other Asian countries such as China (84%). The survival rate is shallow when compared with Western countries such as the US (85%), Sweden (83%), and the United States (88%) [2].

According to studies, the growing incidence of breast cancer in the younger population requires special attention regarding early detection by screening, treatment cost reduction, quality management, enhanced referral pathways, and financial security against the illness [25, 26]. The Government of India established Ayushman Bharat, a comprehensive cashless health insurance plan, for the lower 40% of the population 2018, offering 500,000 per family per year for health care costs. This system has the potential to provide high-quality cancer care by directly tying reimbursement to the evidence-based management guidelines proposed by India's National Cancer Grid, which is critical for a disease where treatment affordability is a significant concern [2, 27-28]. Our study advocated for opportunistic breast cancer screening in public health facilities and a strengthened referral process for early treatment of breast cancer patients.

Limitations

This study has several limitations; being a retrospective study based on a single cancer centre, the sample size and the composition of the patients may limit the analysis from making any generalization to the population or community.

Conclusion and Recommendations

The stage at diagnosis was identified as an essential factor for breast cancer survival. A better survival rate is associated with lower-grade (early-breast cancer), node-negative, non-invasive breast cancer, and women under 50. The overall five-year survival of locally advanced breast cancer and metastatic breast cancer (68% and 57%) was lower than early breast cancer (70%). Thus, higher stages were found to have a poorer prognosis than lower stages. Compared to this, the overall five-year survival of all breast cancer was estimated at 68.7 per cent. The study indicates a higher overall survival rate compared to the national average, and the same can be attributed to various factors, including advances in treatment. The hazard ratio was high with postmenopausal women, multiparous women, and those with invasive breast cancer. The findings of this study highlight the trends in the survival of breast cancer patients in a given context and offer some key insights. The study feeds into ongoing research and policy discussions on the survival of breast cancer patients. Considering the large number of cases (32%) reported in women between 40-49 years of age, focused screening among this age group may improve early detection and survival.

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