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Survival Analysis: A Hospital Based Retrospective Life Span Study of Breast Cancer Patients after First Recurrence

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Abstract

Background

Overall survival of breast cancer patients has been calculated many times but there is no precise research available regarding the survival time of breast cancer patients after recurrence. We investigated the effects factors on mortality due to breast cancer.

Methods

All Factors were analyzed using statistical tools and techniques to find out rate of mortality after recurrence. Descriptive statistics, cox proportional hazard models were used to find statistical significant variables. In the present study recurrence is considered as an important event which may play a role in study of breast cancer progression. In this study, we evaluated breast cancer risk factors in relation to mortality due to this disease among 1028 women with breast cancer in Lahore, Pakistan. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between risk factors and mortality due to breast cancer were estimated in subtype-specific Cox regression models.

Results

Survival of breast cancer patients depends upon many factors. A total of 581 alive and 447 deaths due to breast cancer occurred during a median follow-up period of 1977 days. Median survival time after recurrence was 3 years. Significant factors were included post- menopausal women who diagnosed and had recurrence at the age < 45 of molecular subtype estrogen receptor positive, progesterone receptor negative, Her2.neu positive with tumor size ≥ 3 & involved lymph nodes >5. Radiotherapy has increased life span of patients even after recurrence.

Conclusion

Younger women had higher risk of mortality after recurrence even gone through chemotherapy while lower grade tumor had good prognosis. Radiotherapy played a major role in increasing life time of breast cancer women after recurrence. Our findings are consistent with those from previously published data.

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Introduction

Although with the advancement of diagnostic methods still breast cancer is the most frequently diagnosed cancer in Pakistani women, 1 out 9 women are suffered due to this disease in their life span [1]. Factors like age, race, family history, presence of a BRCA1 or BRCA2 genetic mutation, hormonal factors, history of benign breast disease, and certain lifestyle factors like obesity, weight gain after menopause, alcohol and tobacco consumption may influence on disease progression [2, 3, 7]. Some other studies have documented early puberty, late menopause, contraceptive and/or prevention of miscarriage pills, no pregnancy and no breastfeeding to be associated with adverse prognosis in breast cancer patients [8, 4, 9, 10]. It takes time to diagnose breast cancer due to lack of awareness and availability of health facilities in Pakistan. After diagnosis availability of doctors and time slot to give primary treatment like radiotherapy and chemotherapy may have effect on patients' survival [11, 12].

Breast cancer patients usually experience local, regional and distant recurrence after primary treatment [13, 14, 4]. Literature showed mortality rate of breast cancer was greater for those women who faced recurrence than those without recurrence [15]. Radiotherapy and chemotherapy are used as systematic treatment, sometimes chemotherapy is given before radiotherapy but there is no set standard for given chemotherapy [16, 17]. Epidemiological studies have shown that associations between primary treatment and mortality.

Molecular subtypes of breast cancer have varying survival rates in the clinical context when estrogen and progesterone receptors are not equal in status, estrogen receptor (ER) and progesterone receptor (PR) have proved their importance in treatment decision [18, 19, 20]. In some cases chemotherapy has increased survival time for estrogen receptor negative women [21]. Many researchers reported survival after local recurrence was much inferior for patients with triple-negative breast cancer than for other patients [22, 23]. In published researches 15% to 30% breast cancer cases fall in Her2 positive subtype which has worst prognosis , Her2 (epidermal growth factor gene is located on the long arm of chromosome [24, 25, 26]. The tumor size and number of involved nodes exert a powerful influence on recurrence and mortality [27]. Probability of breast cancer is high in families where any blood relation has cancer history or females' relatives have ovarian or breast cancer history [28]. For therapy decision making purpose it is important not only to study prognosis but also tumors' subtypes and recurrence [29].

Researches are available on overall survival and disease free survival of breast cancer patients, but very few have emphasized on survival time after recurrence [2, 30, 15]. Survival analysis techniques make it easy to interpret highly correlated risk factors of any disease, when censoring occur. Mostly censoring occurred in disease data if at the end of follow up understudy patients are still alive and do not experience event of interest [31].

Many studies have been conducted on breast cancer survival analysis but still in the best of our knowledge not a single one is available on Pakistani population. This analysis, therefore, aims to evaluate the association between breast cancer risk factors and mortality due to breast cancer after recurrence among women in Lahore, Pakistan. This study was undertaken with the following objectives: to find out effect of recurrence on breast cancer patients' mortality after observing different factors at time of primary diagnosis breast cancer, and to identify discordant factors to get in depth details of breast cancer progression.

Materials and Methods

Study Population

We retrospectively reviewed the data of 1028 breast cancer women who have observed recurrence after primary treatment from February, 2011 to February, 2018 in Lahore, Pakistan. Data were obtained from medical record of hospital and phone call interviews. Pathological, clinical and demographic factors were collected from patients' medical record. Phone calls were made to ask about end point which was death due to breast cancer, censored event was still alive or death due to other reasons. Exclusion criteria were male patients of breast cancer, and women did not observe recurrence after primary treatment. Patients with missing data were excluded from analyses. This study did not involve the use of personal identifying information.

Statistical Analysis

Kaplan-Meier estimator have been used to derive the

survival curve, and to get median follow up time, log rank tests showed statistical significance factors for survival after recurrence [32, 33]. Censored event was women still alive at the end of seven years or have died due to other reasons except breast cancer. To evaluate which factors have statically significant effect on survival of breast cancer women after recurrence cox proportional hazard models were employed individually for each understudy variable and multivariate analysis were used to estimate combine effects of understudy factors in seven years survival after recurrence, ninety five percent confidence intervals, and P-values were calculated for hazard ratios. As at the end of follow-up some women were still alive or died due to any other reason, this event was marked as right censoring. All statistical analyses were carried out using R version 3.5.1; a P value below 0.05 was regarded as significant in all analyses.

Results

Different factors were considered to study progression of breast cancer, distribution of prognostic factors was as follows: age at diagnosis (<45 (36.1%), ≥ 45 (63.9%)), age at recurrence (<45 (30.0%), ≥ 45(70.0%)), survival time after recurrence (0-2.99 (49.3%), 3-5.99 (45.8%), ≥ 6 (4.9%)), Family history of breast cancer (No (38.6%), Yes (61.4%)), initial menopause status (Pre-menopause (43.3%), post-menopause (56.7%)), estrogen receptor (Negative (54.1%), Positive (45.9%)), progesterone receptor (Negative (35.4%), Positive (64.6%)), Her2.neu (Negative (47.9%), Positive (52.9%), initial chemotherapy and radiotherapy (No (12.6%), Yes(87.4%) & No (63.6%), Yes (36.4%)), initial tumor size (<3 (63.4%), ≥ 3 (36.6%)), initial lymph nodes involved (≤ 5 (69.3%), >5 (30.7%)) and initial tumor grade (1 (56.7%), 11&111 (43.3%) (Table 1)

Univariate analysis showed age at diagnosis, and age at recurrence <45 have less survival time after recurrence of breast cancer. There was higher rate of mortality for post-menopausal women than pre-menopausal (HR: 1.07, (95%CI: 0.89; 1.29), P= 0.4790) [34].Women who had family history of breast cancer have higher hazard ratio than those who did not have (HR: 1.51, (95%CI: 1.23; 1.84), P= <0.001). Estrogen receptor positive (HR:1.67, (95%CI: 1.38;2.02),P=<0.001), progesterone receptor negative (HR:0.17, (95%CI: 0.14;0.21),P= <0.001) and HER2.neu positive (HR:2.37, (95%CI: 1.94;2.91), P= <0.001) had effected survival after recurrence a lot. Women underwent to Initial chemotherapy had no effect on mortality after recurrence (HR: 2.43, (95%CI: (1.69; 3.50), P= <0.001), while radiotherapy has increased survival (HR: 0.74, (95% CI: 0.60; 0.90), P=0.0025).

Baseline Characteristics (n=581)	(n=447)	(n=1028)	
Age at Diagnosis (Years)	**Alive**	**Death**	**Total**
<45	191 (32.9%)	180 (40.3%)	371 (36.1%)
≥ 45	390 (67.1%)	267 (59.7%)	657 (63.9%)
Age at Recurrence (Years)			
<45	165 (28.4%)	143 (32.0%)	308 (30.0%)
≥ 45	416 (71.6%)	304 (68.0%)	720 (70.0%)
Survival Time after Recurrence (Years)			
0-2.99	156 (26.9%)	351 (78.5%)	507 (49.3%)
3-5.99	378 (65.1%)	93 (20.8%)	471 (45.8%)
≥ 6	47 (8.1%)	3 (0.7%)	50 (4.9%)
Breast Cancer Family History			
No	254 (43.7%)	143 (32.0%)	397 (38.6%)
Yes	327 (56.3%)	304 (68.0%)	631 (61.4%)
Initial Menopause Status			
Pre-Menopause	261 (44.9%)	184 (41.2%)	445 (43.3%)
Post-Menopause	320 (55.1%)	263 (58.8%)	583 (56.7%)
Estrogen receptor (ER)			
Negative	374 (64.4%)	182 (40.7%)	556 (54.1%)
Positive	207 (35.6%)	265 (59.3%)	472 (45.9%)
Progesterone receptor (PR)			
Negative	66 (11.4%)	298 (66.7%)	364 (35.4%)
Positive	515 (88.6%)	149 (33.3%)	664 (64.6%)
Her2.neu			
Negative	330 (56.8%)	154 (34.5%)	484 (47.1%)
Positive	251 (43.2%)	293 (65.5%)	544 (52.9%)
Initial Chemotherapy			
No	99 (17.0%)	31 (6.9%)	130 (12.6%)
Yes	482 (83.0%)	416 (93.1%)	898 (87.4%)
Initial Radiotherapy			
No	351 (60.4%)	303 (67.8%)	654 (63.6%)
Yes	230 (39.6%)	144 (32.2%)	374 (36.4%)
Initial Tumor Size (cm)			
<3	446 (76.8%)	206 (46.1%)	652 (63.4%)
≥ 3	135 (23.2%)	241 (53.9%)	376 (36.6%)
Initial Nodes (n)			
<=5	496 (85.4%)	216 (48.3%)	712 (69.3%)
>5	85 (14.6%)	231 (51.7%)	316 (30.7%)
Tumor Grade			
1	450 (77.5%)	133 (29.8%)	583 (56.7%)
11&111	131 (22.5%)	314 (70.2%)	445 (43.3%)

Table 1: Patient Characteristic.

Tumor sizes greater than >=3 (cm) had poor prognosis to those with tumor sizes (<3 cm) (HR: 2.67, (95%CI: (2.21; 3.22), P= <0.001) Additionally, the risk of death in women were diagnosed breast cancer as a primary

disease who had less than two involved nodes was higher in comparison women with ≤5 initial lymph nodes involved (>5, (HR: 3.78, 95%CI: (3.14;4.57), P= <0.001). Deaths due to breast cancer were higher for women had tumor grade 11&111 as compared to grade 1 (HR=6.15, 95%CI: (4.99; 7.58), P<0.001). (Table 2).

To identify combine effect of significant prognostic factors, a multivariate Cox regression analysis was conducted assuming proportional hazard rate [35]. To find out factors have effect on mortality due to breast cancer among Pakistani females after recurrence, mutual adjustment for age at diagnosis & recurrence, menopause status, family history , estrogen receptor, progesterone receptor, Her2.neu, chemotherapy, radiotherapy, tumor size, nodes and grade at primary diagnosis of breast cancer were taken into consideration. In the multivariable model , factors results were as followed: age at diagnosis [hazard ratio (HR) (95% confidence interval (CI) < 45 years vs ≥ 45 years=0.60 [0.40;0.90] ; P value for trend (P trend)= 0.0136] & recurrence [hazard ratio (HR) (95% confidence interval (CI) < 45 years vs ≥ 45 years= 0.95 [0.65;1.40];P trend=0.8099]; menopause [HR (95% CI) pre-menopause vs post-menopause=1.51 [1.06;2.15]; P trend= 0.0226]; family history of breast cancer [HR (95% CI) no vs yes=0.98 [0.80;1.22]; P trend=0.8830]; estrogen receptor [HR (95% CI) negative vs positive 1.08 [0.89;1.31]; P trend= 0.4532]; progesterone receptor [HR (95% CI) negative vs positive 0.39 [0.31;0.49]; P trend= <0.001]; Her2.neu [HR (95% CI) negative vs positive 2.06 [1.66;2.55]; P trend= <0.001]; Initial treatment chemotherapy [HR (95% CI) no vs yes 1.58 [1.08;2.30]; P trend= 0.0173] & radiotherapy [HR (95% CI) no vs yes 0.78 [0.64;0.97]; P trend= 0.0232]; initial tumor size [HR (95% CI) <3cm vs ≥ 3cm 1.44 [1.18;1.76]; P trend= <0.001]; initial number of involved nodes [HR (95% CI) ≤ 5 vs 5 2.42 [1.97;2.97] <0.001]; initial tumor grade [HR (95% CI) lower vs higher 3.73 [2.98;4.67] <0.001].

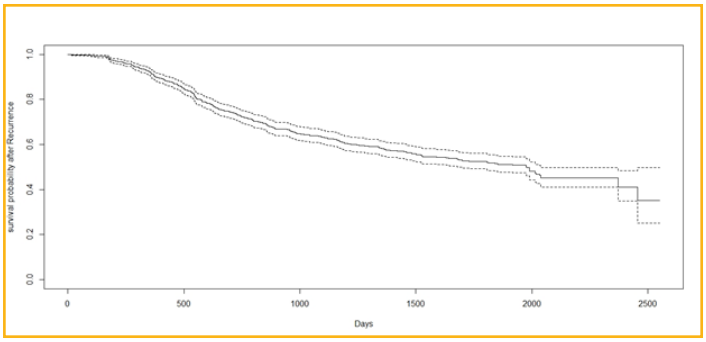
Statistically significant factors were : age at diagnosis and recurrence <45, post-menopause, estrogen receptor positive, progesterone receptor negative, Her2.neu positive, tumor size ≥ 3, lymph nodes >5 and high grade of tumor (11&111). Progesterone receptor negative women had more deaths within 7 years than progesterone receptor positive while chemotherapy has no effect on reduction mortality due to breast cancer after recurrence (Table2).

Factor Univariate Analysis Multivariate Analysis HR 95% CI p Value HR 95% CI p Value
Age at Diagnosis (Years)
< 45 Reference
>=45 0.75 [0.62; 0.91] 0.0033 0.60 [0.40; 0.90] 0.0136
Age at Recurrence (Years)
< 45 Reference
>=45 0.83 [0.68; 1.02] 0.0726 0.95 [0.65;1.40] 0.8099
Initial Menopause Status
Pre-Menopause Reference
Post-Menopause 1.07 [0.89; 1.29] 0.4790 1.51 [1.06;2.15] 0.0226
Family History
No Reference
Yes 1.51 [1.23; 1.84] <0.001 0.98 [0.80;1.22] 0.8830
Estrogen receptor
Negative Reference
Positive 1.67 [1.38; 2.02] <0.001 1.08 [0.89; 1.31] 0.4532
Progesterone receptor
Negative Reference
Positive 0.17 [0.14; 0.21] <0.001 0.39 [0.31; 0.49] <0.001
Her2.neu
Negative Reference
Positive 2.37 [1.94; 2.91] <0.001 2.06 [1.66; 2.55] <0.001
Initial Chemotherapy
No Reference
Yes 2.43 [1.69; 3.50] <0.001 1.58 [1.08; 2.30] 0.0173
Initial Radiotherapy
No Reference
Yes 0.74 [0.60; 0.90] 0.0025 0.78 [0.64; 0.97] 0.0232
Initial Tumor Size (cm)
<3 Reference
≥ 3 2.67 [2.21; 3.22] <0.001 1.44 [1.18; 1.76] <0.001
Initial Nodes Involved (n)
≤ 5 Reference
>5 3.78 [3.14; 4.57] <0.001 2.42 [1.97; 2.97] <0.001
Initial Tumor Grade
1 Reference
11&111 6.15 [4.99; 7.58] <0.001 3.73 [2.98; 4.67] <0.001

Table2: Univariate and multivariate cox regression analysis

Hazard ratio (HR) for association of factors with mortality due to breast cancer after recurrence HR hazard ratio, CI confidence interval, P-value.

Kaplan-Meier curve for the associations between breast cancer risk factors and survival time after recurrence among 1028 women diagnosed and treated before recurrence in Lahore, Pakistan.



Kaplan–Meier estimates of time to death
Figure 1: Kaplan-Meier Survival Curve.

Discussion

This study was conducted on 1028 breast cancer cases from a hospital-based case series in Lahore, Pakistan, All the information about demographic, risk factor, pathology, and follow-up data was collected to study association between these factors and mortality among breast cancer women. We found differences in the age at diagnosis and recurrence, menopause status, family history of breast cancer, estrogen receptor, progesterone receptor, Her2.neu, chemo & radiotherapy, tumor size, involved lymph nodes and tumor grade across mortality of patients. In general, younger age, post-menopause, larger tumor size, greater number of involved nodes and higher grade seem to show higher rate of mortality among breast cancer women after recurrence.

Age of patients at diagnosis time was the most important factor effecting survival. Relationship between breast cancer death rate and age has been controversial topic for many researchers [36, 34, 8]. We divided age into two classes; the median age at diagnosis was 47 years while for recurrence it was 49 years which are similar to those found in other studies [32]. It is not clear which factors contributed to the relatively poor prognosis in young women [36]. In one study, average survival time after recurrence occurred within 3 years, poor prognosis was ≥ 6 (4.9%) years survival rate after recurrence. Women with early-onset breast cancer are more likely to experience a recurrence and once they do, are more likely to succumb to their disease [4]. Analysis depicted, after recurrence age group < 45 years old women have high risk for death than age groups ≥ 45. Our results are consistent with early age of onset being a risk factor for local recurrence [14, 32]. Other important factors included tumor ≥ 3cm size, lymph nodes > 5. Estrogen and progesterone status were classified according to the examination of the primary tumor results, our study has emphasized prognostic factors at the time of diagnosis. In univariate analysis, prognosis was worst in women who recurred even after receiving chemotherapy and had family history of breast cancer; however family history was not significant in multivariate model [37]. We did not include information of treatment after recurrence, as many studies reported that chemotherapy after recurrence was effective to increase survival time. Post-menopausal women have estrogen receptor and HER2. neu positive with progesterone receptor negative have not been through radiotherapy had increased risk of deaths after recurrence within seven years, which justify previous published results [4, 38, 39,]. In this research, the number of involved nodes, grater tumor size and tumor grade 11&111 were important factors to study the probability of deaths after recurrence in women diagnosed breast cancer. It is highly recommended to add hormone therapy and trastuzumab in systematic treatment to get in depth analysis. Our research finding has opened new avenues for clinicians to study breast cancer progression in Pakistani women. In conclusion, our data indicate that risk factors for breast cancer are differentially associated with mortality due to this disease after recurrence. These findings are supportive of the prognostic value of risk factors associated with mortality and could have implications for clinical counseling and for decision about treatment at initial level. Future prospective studies are needed on breast feeding, menarche and body mass index to delineate the role of all the factors associated with progression of breast cancer [40, 41, 42, 43, 44].

Compliance with Ethical Standards

The study was approved by the Departmental Ethics Committee of CSAS, Lahore, Pakistan. After complete explanation of the study objectives to the oncology department INMOL hospital, Dr. Waqas Fazil from INMOL hospital provided all the required data. Data were provided under the agreement that no personal information will be disclosed and data will be used only for research purpose. A written consent was taken from hospital after completing data collection.

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Conflict of interest

The authors declared no conflict of interests related to the subject matter or material discussed in the manuscript.

Ethical approval

The study was approved by the Departmental Ethics Committee of CSAS, Lahore, Pakistan.

Informed consent

Participants had rights to not give information.

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