RESEARCH COMMUNICATION

Variables Associated with Recurrence in Breast Cancer Patients-the Shaukat Khanum Memorial Experience

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Abstract

From a cohort of female breast cancer patients registered at the Shaukat Khanum Memorial Cancer Hospital and Research Center, in Lahore, Pakistan, during the time period extending from December 1994 to December 2002, 700 subjects who were followed up in time, were selected. Those who presented with benign tumors, carcinoma in situ, or metastases were excluded from the analyses. Age, tumor size, nodal status, menopause, estrogen receptor (ER), and progesterone receptor (PR) status, at the time of presentation, were determined. Tumors were classified according to the TNM classification (American Joint Commission on Cancer (AJCC)-sixth edition), and subsequently, grouped into T1/T2 and T3/T4. Lymph nodes were categorized as N0 (node-negative) and N1, N2, and N3 combined (node-positive). The odds ratio (OR) for developing recurrence in T3/T4 versus T1/T2 was determined to be 2.06 (95% confidence interval (CI) 1.39-3.05, $p < 0.001$); the OR for node-positive relative to node-negative was found to be 2.54 (95 % CI 1.61-4.0, $p < 0.001$). Furthermore, the association between the odds of developing recurrence in ER-positive compared to ER-negative was represented by an OR of 0.61, (95 % CI 0.40-0.94 (p=0.02)). These findings are consistent with the observations that ER-positive, node-negative, and T1/T2 lesions have a decreased risk of recurrence. Also, ER-positive patients may have a better response to hormonal treatment than those who are ER-negative.

Key Words: Breast cancer - recurrence - tumor size - nodal status - estrogen receptor.

Asian Pacific J Cancer Prev, **6**, 54-57

Introduction

Latest estimates suggest that approximately 1,050,000 new breast cancer cases occur worldwide annually (Stewart and Kleihues, 2003a). Of these nearly 470,000 cases are seen in developing countries and the remainder in developed nations (Stewart and Kleihues, 2003b). In 1998, 412,000 deaths were attributed to breast cancer, accounting for 1.6 percent of all female deaths worldwide. Of these, 250,000 (61%) deaths occurred in developing countries (Stewart and Kleihues, 2003c).

The age-adjusted breast cancer incidence is very high in the United States (US), United Kingdom (UK), and Australia, where it has been measured to be more than 80 per 100,000 population per year (Stewart and Kleihues, 2003d). Breast cancer is the commonest malignancy in the US with the age-adjusted incidence rate being 134.75 per 100,000 population in the year 2001 (Surveillance, Epidemiology, and End Results (SEER, 2004)). However, breast cancer rates are five times higher in the US than in many countries of Asia and this fact may be attributed to differences in lifestyle as wells to some extent to differences in expression of estrogen receptors in the mammary cells (Lawson, 1999).

At the Shaukat Khanum Memorial Cancer Hospital and Research Center, (SKMCH and RC), breast cancer has been the leading cause of morbidity at the hospital since its inception in December 1994. The total number of breast cancer cases in adult females registered from December 1994 to December 2002 was 3,889.

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Materials and Methods

Population for Analysis

Of these 3,889 patients, the 2,328 in the database included patients with breast cancer who had undergone surgical resection of the tumor followed by adjuvant treatment and for whom pathology reports were available. The diagnoses had been made either at the Shaukat Khanum Memorial Cancer Hospital and Research Center or at a cancer reporting facility other than this. Of the total, 1,749 were non-metastatic (M0), 540 metastatic (M1), and 39 not assessable (MX). M1 and MX were excluded from the study. Among 1,749 cases remaining, another 579 (33.1 %) who were lost to follow-up were also removed. In all, two patients without any evidence of primary tumor (T0), 326 in whom primary tumor could not be assessed (TX), 7 with ductal or lobular carcinoma in situ (Tis), and 326 in whom regional lymph nodes could not be assessed (NX), were also removed. Many observations were taken out because of missing values; these included 90 for unknown menopausal status, 109 for unknown estrogen receptor (ER) status, and 7 for unknown progesterone receptor (PR) status. Hormone receptor status was determined by immunoperoxidase assay. Analyses in this report also excluded the 11 subjects whose self report of remission could not be verified. Finally, analyses were conducted on 700 patients with invasive breast cancer for whom complete information on variables under study was available. Malignant neoplasms of the female breast, categorized as 174 by the International Classification of Diseases, Ninth revision, Clinical Modification, (ICD-9-CM), were included in the study. This study was approved by the Scientific Review Committee at SKMCH and RC.

Variables in the Study

For the logistic regression study, the outcome was dichotomized into relapse (code 1) versus remission and death without relapse (code 0). The end point of interest for these analyses was recurrence. The predictors taken into consideration were age, tumor characteristic, nodal status, menopausal status, and ER and PR status. Tables 1-2 represent variables evaluated for their possible associations with the outcomes of interest along with the codes applied to them and their distributions in the study.

Table 1. Variables Evaluated for Possible Association with Recurrence Among Invasive Breast Cancer Patients

Variable type	Variable	Description
Binary	Tumor size	T1/T2=0 (referent) T3/T4=1
	Nodal involvement	N0=0 (referent) N1/N2/N3=1
	ER status	ER negative=0 (referent) ER positive=1
	PR status	PR negative=0 (referent) PR positive=1
	Menopausal status	Premenopausal=0 (referent) Post-menopausal=1
Continuous	Age	21-89 years

Statistical Analyses

Univariate analysis using the logistic regression equation was used to determine an association between age, which was the only continuous variable, and recurrence. It was found to be substantially significant ($p = 0.004$).

Bivariate analyses were used to determine relationships between categorical predictors and breast cancer outcomes using the Pearson chi-square analyses. In bivariate analyses, all of the abovementioned factors except PR status were found to be significantly associated with differences in outcomes (Table 3).

For multivariate analysis, those predictors which showed significant results in the preceding analyses were entered in the forward stepwise fashion in the regression model. Logistic regression model was used to study the odds of developing recurrence; p values for heterogeneity of odds ratio were calculated using the likelihood ratio statistics. Statistical Package for Social Sciences (SPSS) 10.0 was used to run all the analyses.

Results

The subjects ranged in age from 21 to 89 years (SD 11.3) at the time of presentation at SKMCH and RC. The mean age at presentation was 46.2 years and the median age, 45 years. These figures were close to those for the age characteristics of the 2,328 cases, from whom these 700 evaluable patients were selected. Figure 1 shows the distribution of age for the 700 subjects in the study.

In logistic regression, using the forward stepwise (Likelihood Ratio (LR)) method, the authors systematically

Table 2. Distributions of Variables in the Study

Variable	Recurrence Count= (147); %	Remission/Death Count= 553; (%)	Total Count (n=700); %
T1/T2	80 (54.4)	414 (74.9)	494 (70.6)
T3/T4	67 (45.6)	139 (25.1)	206 (29.4)
N0	28 (19.0)	217 (39.2)	245 (35.0)
N1/N2/N3	119 (81.0)	336 (60.8)	455 (65.0)
ER-negative	109 (74.1)	345 (62.4)	454 (64.9)
ER-positive	38 (25.9)	208 (37.6)	246 (35.1)
PR-negative	80 (54.4)	278 (50.3)	358 (51.1)
PR-positive	67 (45.6)	275 (49.7)	342 (48.9)
Premenopausal	90 (61.2)	274 (49.5)	364 (52.0)
Postmenopausal	57 (38.8)	279 (50.5)	336 (48.0)

Table 3. Bivariate Analyses Showing Relationship Between Variables Mentioned and Outcomes

Variable	X2	df	Sig
Tumor characteristic	23.37	1	<0.001
Nodal involvement	20.81	1	<0.001
ER status	7.05	1	0.008
Menopausal status	6.34	1	0.012
PR status	0.80	1	0.371

Table 4. Forward Stepwise Logistic Regression (likelihood ratio) Analyses

Variable	Step1 beta Sig OR	Step2 beta SigOR	Step3 beta SigOR	Step4 beta SigOR	Step5 beta SigOR
Tumor size	.914 .000 2.49	.80 .000 2.22	.756 .000 2.13	.790 .000 2.20	.790 .000 2.20
Nodal involvement		.89 .000 2.45	.886 .000 2.42	.917 .000 2.50	.917 .000 2.50
Age			-.020 .024 0.98	Removed*	Not entered**
ER status				-.561 .009 0.57	-.561 .000 0.57
Menopause				Not entered**	Not entered**
Constant	-1.64 .000 .19	-2.24 .000 0.11	-1.31 .004 0.27	-2.08 .000 0.13	-2.08 .000 0.13
-2 Log-Likelihood	697.436	680.668	675.453	673.410	673.410
Likelihood Ratio Test (df)	22.103 (1)	16.768 (1)	5.215 (1)	7.258 (1)	7.258 (1)
Significance	<0.001	<0.001	0.022	0.007	0.007
Model Chi Sq. (df)	22.103 (1)	38.871 (2)	44.087 (3)	46.129 (3)	46.129 (3)
Significance	<0.001	<0.001	<0.001	<0.001	<0.001

*Removed because of a POUT (Probability Out) criterion of 0.10.
**Did not fulfill the 0.05 PIN (Probability In) criteria of entry into the model.

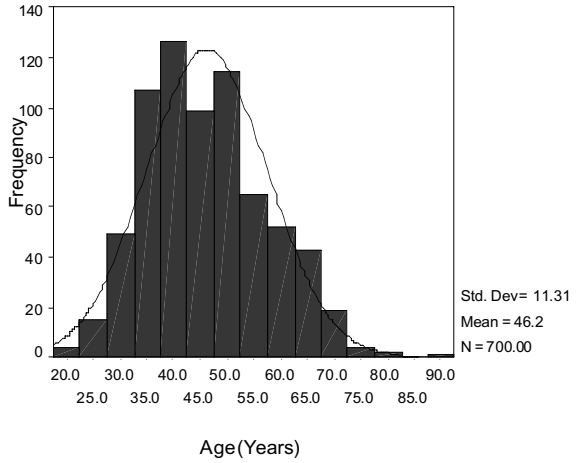

Figure 1. Age Distribution of the 700 Subjects

adjusted for tumor size, nodal involvement, age, ER status, and menopausal status.

The regressors, tumor characteristic and nodal involvement were entered in the first and second steps, respectively. Each was found to be significantly associated with recurrence ($p<0.001$). In the subsequent stage, age was added and a substantial negative association between age and relapse was revealed. In the next phase, ER status was entered; ER status adjusted for tumor characteristics and nodal involvement showed appreciable differences in recurrence as measured by the odds ratio. In this step, age was removed as a predictor as it did not fulfill the criteria for retention into the model. In the final step, menopausal status was added as a predictor but no significant relationship could be established between it and recurrence of breast cancer. In the overall model, tumor characteristic (OR 2.2, 95 % CI 1.5-3.24), nodal involvement (OR 2.5, 95 % CI 1.59-3.94), and ER status (OR 0.57, 95 % CI 0.38-0.87) were the only predictors which showed statistically significant associations with the outcome of interest. Table 4 shows the order in which the variables were entered in the statistical model; it also gives a summary of those variables which were either not entered or removed because of the inclusion/exclusion criteria set for the model. The likelihood ratio test which was conducted by subtracting the statistic for the full model from that of the reduced model showed marked change in all the steps except the last one in which menopause was added as a regressor to the model.

Discussion

Studies have determined that histologic grade, lymph node involvement, and hormone receptors are significant univariate prognostic factors in invasive breast cancer (Lee et al, 1997a). Tumor size and lymph node status have been found to act as independent but additive prognostic factors for breast cancer decreasing survival independent of one another (Carter et al, 1989). The results in our study have reinforced the findings reported earlier pertaining to tumor characteristics, lymph node involvement, and hormone receptor status as being important prognosticators in breast cancer recurrence. Favorable prognostic factors include tumor size equal to or less than 2 cm and positive ER/PR status (Wong et al, 1992; Figueroa, 1993). Palpable tumors have bad prognosis than mammographically detectable tumors (Lee et al, 1997b). Whereas many studies have suggested the lymph node negative status to be a strong predictor of survival in breast cancer patients, one has suggested that it is unlikely (Moorman et al, 2001). Further, it has been documented that estrogens play an important role in regulating the growth and differentiation of normal, premalignant, and malignant cell types, especially breast epithelial cells through interactions with two nuclear estrogen receptors (α-ER$^-$ and β-ER$^-$) (Platet et al, 2004a). ER and PR have been studied in breast cancer for more than 2 decades now (Platet et al, 2004b). Clinical and experimental data have demonstrated the importance of ER in the development and prognosis of breast cancer (Platet et al, 2004c). The association of ER-positive findings with improved clinical course was recognized as early as in 1977 and it has been shown that the disease free survival (DFS) and overall survival (OS) are better in patients with ER-positive status (Donegan, 1992). Some studies have shown the disease free interval (DFI) to be longer in patients with ER-positive than in ER-negative, independent of axillary

nodal status (Brdar et al, 1988). Another study has shown the difference in DFI between ER-positive and ER-negative groups not to be significant, whereas, that between PR-positive and PR-negative to be significant (Gelbfish et al, 1988; Morimoto et al, 1988). The ER-positive breast cancer may be considered a distinct sub-population of breast cancer exhibiting a high response rate to endocrine therapy. Treatment of breast cancer has already been divided by hormone receptor status and hormonal agents are only used in receptor-positive cancers (Colditz et al, 2004). Moreover, the prognostic effect of young age on disease relapse has remained controversial in the past (Chung et al, 1996). However, some studies have reported poor survival in young patients as compared to older counterparts (Yildirim et al, 2000). Also, it has been documented that women who develop breast cancer at a young age have a higher risk of developing cancer in the contralateral breast than older women (ACS, 2001). There are some studies which have suggested that differences in biologic characteristics of breast cancer in premenopausal women versus post-menopausal women may account for differences in prognosis (Chia et al, 2004, Melinda et al, 2003), whereas, other studies report similarity in aggressiveness in young patients and older age groups (Gillet et al, 1997). It can be said that the traditionally unfavorable clinicopathologic features in operable breast cancer are large tumor size, axillary node metastases, and perimenopausal status (Jotti, 1991). However, our study failed to capture perimenopause as an unfavorable factor for relapse of breast cancer. The results in this study also reinforce those in another study according to which axillary nodal status, tumor size, and hormone receptor status are established prognostic factors in breast cancer (Morabito et al, 2003). Although the results of our study should be interpreted with caution, they may suggest that selection of adjuvant treatments in our setting may delay the onset of recurrence of breast cancer in patients who are in remission following surgical treatment.

Acknowledgements

I wish to acknowledge the contribution of all the Outcomes Researchers of the Shaukat Khanum Memorial Cancer Hospital and Research Center who have worked on the breast outcomes analyses project for data entry leading to completion of this study.

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