RESEARCH ARTICLE

Prognostic Factors for Survival in Patients with Breast Cancer Referred to Omitted Cancer Research Center in Iran

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Abstract

Background: Breast cancer is a malignant tumor that starts from cells of the breast and is seen mainly in women. It's the most common cancer in women worldwide and is a major threat to health. The purpose of this study was to fit a Cox proportional hazards model for prediction and determination of years of survival in Iranian patients. Materials and Methods: A total of 366 patients with breast cancer in the Cancer Research Center were included in the study. A Cox proportional hazard model was used with variables such as tumor grade, number of removed positive lymph nodes, human epidermal growth factor receptor 2 (HER2) expression and several other variables. Kaplan-Meier curves were plotted and multi-years of survival were evaluated. Results: The mean age of patients was 48.1 years. Consumption of fatty foods (p=0.033), recurrence (p<0.001), tumor grade (p=0.046) and age (p=0.017) were significant variables. The overall 1- year, 3-year and 5-year survival rates were found to be 93%, 75% and 52%. Conclusions: Use of covariates and the Cox proportional hazard model are effective in predicting the survival of individuals and this model distinguished 4 effective factors in the survival of patients.

Keywords: Breast neoplasms - Cox model - proportional hazards models - survival analysis - Iran

Introduction

Breast cancer (BC) is a malignant tumor that starts from cells of the breast. A malignant tumor is a group of cancer cells that can grow into surrounding tissues or other organs. BC occurs mainly in women (WHO, 2013). one out of every 10 cases is BC (Varughese et al., 2015). The age standardized incidence rate of the disease is as follows: North America, 126 (Toriola et al., 2013), Turkey 35.8 (Kayhan et al., 2014) and Russia 43.2 (Troisi et al., 2012) per 100,000 people.

BC is the most common health problem in Iranian women that its incidence is increasing rapidly. It is the Fifth cause of death and third burden of disease among women malignant disease (Mohammadi et al., 2013). This cancer is the most common cancer in women in the Iranian city of Isfahan, with incidence rate of 30 per 100,000 women (Movahedi et al., 2012) and the mean age of patients was estimated 47 to 50 (Movahedi et al., 2012). Various studies recognized factors like genetic (Afsharfard et al., 2013), duration of breastfeeding, birth rate, number of cigarettes smoked and the duration of it (Fredslund et al., 2012), family history of cancer, the number of abortions(Bjerkaas et al., 2013) and some other factors affected the disease.

Survival analysis is the analysis of the time elapsed between the moment of identification and completion of following patients. The final event can be a death, failure, relapse, or ending the individual's participation in the study. In such analysis, there are two important points: First, the data obtained in this analysis is skewed. The standard methods that assume the data are normally distributed are not useful. The other is that there is censorship in such data. When a patient is considered to be censored if until his presence at study the final event do not happen. Cox proportional hazards regression introduced in 1980 by Kalbfleisch (Kleinbaum, 2012). Proportional hazards means that the Hazard Ratio of the occurrence of events is constant over time, In other words, the risk for an individual, is the ratio of risk to another person, and this ratio does not change over time (NCSS, 2012).

Materials and Methods

The 366 patients with breast cancer (BC), in Cancer Research Center of Shahid Beheshti University of Medical Sciences were considered as the population. Patients were identified from 1998 until 2013, and monitored by cancer research center teamwork. Because the data were missing for some patients, in coordination and permission of cancer research center missing items completed through telephone or contact with patients. The final outcome

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examined in this study is the final survival of patients with BC. The variables examined in this study are age, number of pregnancies, fatty food consumption, type of cancer surgery, tumor grade, recurrence of cancer, tumor size, number of removed positive lymph node, family history, number of abortion, cancer stage and Human Epidermal growth factor Receptor-2 (HER2). One that furnishes more than 35 percent of its total calories from fats, have fatty food consumption (The American Heritage, 2015). Tumor grade is a description of the morphological features of tumor cells in terms of the shape and texture and how abnormal it looks under the microscope which is divided into three grades as well. Tumor cells and tumor tissue with a first class compared to third class are normal and less likely to grow and be aggressive. The grade of the tumor is marker of tumor malignancy (National Cancer Institute, 2013). HER2 is a protein, which plays an important role in BC progression. So, this protein was evaluated in patients which has been reported as positive and negative (Breast Cancer, 2015). Breast surgery can be done in two ways, in first one which is called Breast-Conserving Surgery (BCS), only the tumor and some surrounding tissue is removed and natural breast shape is preserved. In the second type called Modified Radical Mastectomy (MRM) the entire breast is removed (Acil et al., 2014). Data analysis was performed using spss version 20 and Cox proportional hazard models was fitted to the data. Test results were considered to be significant at 5% level.

Table 1. Baseline Characteristics of the Patients

Variable	Category	No (%)	Survival mean (% of death)
Fatty food consumption	Yes	217 (59.3)	63.39 (21.196)
	No	149 (40.7)	44.85 (4.02)
Type of cancer surgery	BCS	236 (64.5)	48.81 (5.93)
	MRM	130 (35.5)	68.61 (29.23)
Tumor grade	1	43 (11.7)	56.82 (4.65)
	2	210 (57.4)	58.96 (12.85)
	3	113 (30.9)	49.76 (20.35)
Recurrence	Negative	59 (16.1)	55.10 (25.42)
	Positive	307 (83.9)	59.71 (12.05)
Tumor size	less than 2	137 (37.4)	54.24 (6.56)
	42039	170 (46.4)	58.12 (14.11)
	More than 5	59 (16.1)	53 (32.2)
Number of removed positive lymph nodes	0	184 (50.3)	61.63 (5.97)
	3-Jan	100 (27.3)	50.3 4 (13)
	4-Feb	34 (9.3)	55.98 (2.94)
	More than 6	48 (13.1)	45 (37.5)
Family history	First level	50 (13.7)	44.39 (16.6)
	Second level and more	48 (13.1)	64.36 (16.6)
	Negative	268 (73.2)	56.45 (13.43)
History of abortion	negative	237 (64.8)	57.67 (13.08)
	Positive	129 (35.2)	52.47 (16.27)
HER2	Negative	276 (75.4)	53.45 (18.18)
	Positive	90 (24.6)	63.71 (22.22)
Stage of cancer	1	91 (24.9)	56.82 (4.39)
	2	172 (47)	58.96 (9.88)
	3	103 (28.1)	49.76 (30.09)

Table 2. Results of Cox Proportional Hazards Model for Assessing the Effect of Different Factors on Breast Cancer Patients Survive

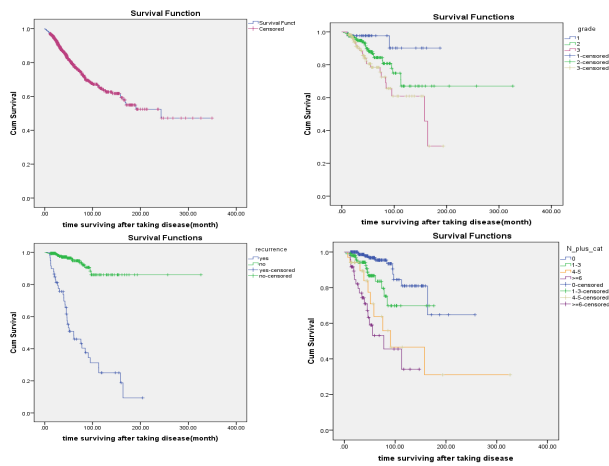| Variable	category	Hazard Ratio	P-value subgroup	P-value Total
Fatty food consumption	Yes	2.83	-	0.033
	No	REF	-	
Type of cancer surgery	BCS	REF	-	0.178
	MRM	0.596	-	
Tumor grade	1	REF	-	0.046
	2	2.16	0.343	
	3	4.2	0.079	
Recurrence	Negative	REF	-	<0.001
	Positive	10.91	-	
Tumor size	less than 2	REF	-	0.985
	42039	0.98	0.969	
	More than 5	0.92	0.889	
Number of removed positive lymph nodes	0	REF	-	0.114
	3-Jan	2.76	0.055	
	4-Feb	3.31	0.069	
	More than 6	5.1	0.016	
Family history	First level	1.59	0.305	0.246
	Second level and more	1.9	0.13	
	Negative	REF	-	
History of abortion	negative	REF	-	0.215
	Positive	0.63	-	
HER2	Negative	REF	-	0.178
	Positive	0.62	-	
Stage of cancer	1	REF	-	0.85
	2	0.7	0.654	
	3	0.83	0.847	
Age	-	1.03	-	0.017
Number of pregnancy	-	1.01	-	0.907

Figure 1. Kaplan-Meier curve for Survival time, Tumor Grade, Number of removed positive lymph nodes and Recurrence disease

Results

Data from 366 female with BC were included to the study. The mean (SD) patients age was 48.13 (10.77) ranged from 17 to 84 years. The mean (SD) number of pregnancies in patients was 3 (1.96). Among them, 40.7% stated that they did not consume fatty foods. Patients with grade 2 tumors and with tumor size of 2-4 cm had the most frequency in their subgroups. Although 16% of patients had recurrence of disease after treatment or surgery (Table 1).

The purpose of this study was to identify prognostic factors associated with survival in patients with BC. The Cox proportional hazard models were fitted to the data (Table 2). Then Kaplan-Meier curves were plotted for some variables. (Figure 1).

Significant variables were fatty foods, recurrence, tumor grade and age of the patient. Patients who tend to eat more fatty foods than those who do not eat fatty foods were 2.83 times more likely to die from the disease. Variable recurrence of cancer was significant (p-v<0.001) and patients who suffer from recurrence after treatment or surgery are 10.91 times more at risk of death from BC than patients who have never had a relapse. One year aging, increases the relative risk of death by BC by 3% and the overall 1- year, 3-year and 5-year survival rate was found as 93%, 75% and 52%.

Discussion

Breast cancer(BC) is a malignant tumor that is observed mainly in women. In this study, Cox proportional hazard models was fitted to the data of BC. Significant variables were consumption fatty food, grade of tumor, age of patient and recurrence of disease. Variables of fatty food is significant and in accordance with Kruk results(Kruk, 2014), although Brennan and et al found no significant association between fat intake and survival of BC patients (Brennan et al., 2015). The number of removed positive lymph node surgery was not statistically significant. However, this variable in patients with more than 6 removed positive lymph nodes is significant. The

risk of patients shows that the number of lymph node surgery increases the relative risk of death from the disease. Plotted Kaplan-Meier curves showed the same results. Similarly, such a relationship has been observed in the study of Gao and et al (Gao et al., 2014). They showed that the relative risk of death from BC for patients with ten and less than ten lymph nodes removal surgery was 57% (p<0.001). Moghadami Fard and et al also studied the relationship between lymph node and predicting the risk of metastasis. They concluded that more than 10 lymph nodes is a factor in predicting the risk of metastasis (Moghadami et al., 2013). In this study, the patient's age is significant with relative risk of 1.03. Aydogan and et al as well as Varughese and et al have shown a significant relationship between survival and age (Aydogan et al., 2015; Varghese et al., 2015). The mean age of diagnosis is 48.5 years in Iran that is consistent with results of previous studies (Haghighat et al., 2013). In this study, the overall 1- year, 3-year and 5-year survival rate was found as 93%, 75% and 52%. which are consistent with result of the 5-year survival of Akbari et al. (Shah et al., 2011) with 76.6 percent, Karimi et al (Akbari et al., 2006) with 75 percent and movahedi and et al. (Movahedi et al., 2012) with 71 percent. In this study HER2 association with the survival of BC patients was not significant. However karimi and et al knew the role of this protein affective in treatment and survival in patients (karimi et al., 2014). Variable recurrence is highly significant. Even patients who experience cancer recurrence after treatment or surgery 11.33 times are more at risk of death from BC. The grade of tumor is a measure of tumor malignancy. Patients with tumor grade Two, compared with patients with tumor grade one, has 59% more risk of death from cancer. The patient whose tumor grade is 3, has 4.2 times more risk of death from BC compared to patient with tumor grade 1. Rosenberg and et al acknowledged the influence of the tumor on survival of patients. They concluded that with increasing tumor grade, the relative risk of death from BC increases (Rosenberg et al., 2005).

In conclusion, using covariates in the Cox proportional hazards model to predict the survival of patients with BC is effective. If the proportional hazard assumption is rejected for some variables, it should be extended to other models of Cox. This model has identified four factors in the survival of patients.

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