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Original Article

Evaluation Factors Affecting on Recurrence, Metastasis, and Survival of Breast Cancer in Iranian Women by Multi-State Model Approach

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Abstract

Background: We used the multistate model to investigate how prognostic factors of breast cancer are seen to affect the disease process.

Methods: This cohort study was conducted at Motamed Cancer Institute of Tehran, Iran on 2363 breast cancer patients admitted from 1978 to 2017, and they were followed up until 2018. We applied the multistate models, including four states: diagnosis, recurrence, metastasis, and final absorbing mortality state.

Results: Age over 50 years, positive lymph nodes and tumor size intensified the hazard of transition from diagnosis to metastasis (P=0.002, P<0.001 and P=0.001 respectively) and they also intensified the hazard of transition from diagnosis to mortality (P=0.010, P<0.001 and P<0.001 respectively). At the same time, the educational level decreased the hazard of mentioned transitions (P<0.001). Positive estrogen receptors reduced the hazard of transition from diagnosis to metastasis (P=0.007) and positive lymph nodes also intensified the hazard of transition from metastasis to mortality (P=0.040). Tumor size had an increasing role in the transitions from diagnosis to recurrence, recurrence to metastasis, and metastasis to mortality (P=0.014, P=0.018 and P=0.002 respectively).

Conclusion: Multistate model presented the detailed effects of prognostic factors on progression of breast cancer. Implementing early diagnosis strategies and providing informational programs, especially in younger ages and lower educational level patients may be helpful in reducing the hazard of transition to higher states of breast cancer and increasing the survival of Iranian women with breast cancer by controlling tumor size growth, lymph nodes involvements and estrogen receptor status.

Keywords: Multistate models; Breast cancer; Transition probability; Survival analysis

Introduction

Worldwide, breast cancer is the most common cancer in women and one of the most important public health problems (1). After lung cancer, breast cancer is the second leading cause of mortality from cancer and after skin cancer, it is the most prevalent cancer among women (2). There are about 1.5 million new cases of breast cancer

diagnosed every year throughout the world, representing 25% of all women with cancer (3).

In Iran, about 16% of all cancers are related to breast cancer. Iranian women get the disease at least a decade earlier than women in developed countries (4, 5). Unfortunately, breast cancer is more commonly diagnosed in advanced stages in Iran, and the epidemiology and histopathology of breast cancer in Iranian patients are different from neighboring countries (6).

Due to earlier diagnosis and improvements in treatment effectiveness, breast cancer survivors are considerably increasing (7). Consequently, a rising number of women are at risk of developing breast tumor recurrence or metastasis (8). Despite advances in the treatment of primary breast cancer, 20-30% of patients experience distant recurrence (9). The importance of studying these different states of breast cancer is that the risk of developing a recurrence is substantially higher than the risk of developing primary breast cancer (10), and the main leading causes of mortality in breast cancer are tumor invasion and metastasis (11). Patients who have experienced metastasis have shorter lifespans than other patients (12). Also, when recurrence occurs, the disease remains nearly incurable. The median survival of patients with metastasis after breast cancer was 2 to 3 years (13). Therefore, in the process of identifying and treating this disease, recognizing factors affecting the incidence of types of recurrences, i.e., local recurrences and metastasis, and examining the relationship between them is crucial among breast cancer patients (14, 15).

In longitudinal time-to-event studies, advanced statistical methods are necessary to analyze the progression of different disease complications. The multistate model is an advanced statistical model that describes the changes in disease status continuously. It deals with the process of patient's movement through a finite number of states simultaneously (16). It is unnecessary to have only one starting state and one end state and patients can pass through more than one intermediate states (17).

In recent years, researchers have become increasingly interested in multistate models and have used it to examine the relationship between various disease intermediate states and the final event in order to gain a deeper understanding of the disease process (16). Using this model, we can also estimate the rate of progression, assess the effects of individual risk factors, and evaluate the hazard ratios or predictive forecasting (15, 18).

The current research demonstrated the probability of transfer to recurrence, metastasis, and mortality and also to examines the impact of significant risk factors such as age, lymph nodes (LN), educational level, estrogen receptor status (ER), and tumor size on the occurrence of different outcomes using a homogeneous Markov time-continues multistate model.

Materials and Methods

This study was a historical cohort study that used the information of female patients with breast cancer admitted at Motamed Cancer Institute (MCI), specialized breast cancer research center, Tehran, Iran. This research institute is a non-governmental multidisciplinary center for breast cancer in Iran.

Data were collected from all women with breast cancer referred to the Motamed Cancer Institute from 1978 to 2017. Inclusion criteria were recording the clinical diagnosis of cancer. Patients were followed up until 2018, and the latest status of patients was received by phone call and registered in the prepared checklists. Also, if necessary, patients were invited to visit in person or send the required documents by mail. Individuals whose final status information was not available and could not be contacted were considered censored. Our final sample size consisted of 2363 breast cancer patients. The final absorbing state was considered patient mortality with intermediate outcomes of recurrence and metastasis.

Informed consent was obtained from all participants. The ethical approval for this study was obtained from Tarbiat Modares University of Iran (no. IR.MODARES.REC.1399.180).

Variables

Age at diagnosis, lymph node (LN), educational level, estrogen receptor (ER), and tumor size were checked to include in the final statistical model as prognostic factors (3, 19-21). Time of diagnosis, recurrence, metastasis and mortality were used to construct time to events for the complications states of breast cancer for the multistate model.

Statistical analysis

In survival analysis, it is usual to model the progression of a disease that can occupy several states over time (e.g., alive without disease, recurrence, metastasis, mortality). Studies analyzing complex disease behavior often use multistate models that have been extensively developed over the last few decades (22).

Multistate models can be used to model the transition of patients among the various states. In these models, issues of interest include estimating progression rates, assessing the effects of individual risk factors, hazard ratios of transitions between disease complications, or prognostic forecasting (23).

This study used a multistate time-to-event model as the main statistical method for modeling, incorporating three transient states and a final absorbing state. (State 1: breast cancer diagnosis, state 2: recurrence, state 3: metastasis, and state 4: mortality). We assumed that a continuous-time homogenous Markov process explores the transition intensity times between these finite complication states in breast cancer patients. The suitable theoretical multistate model for the study was considered as Fig. 1.

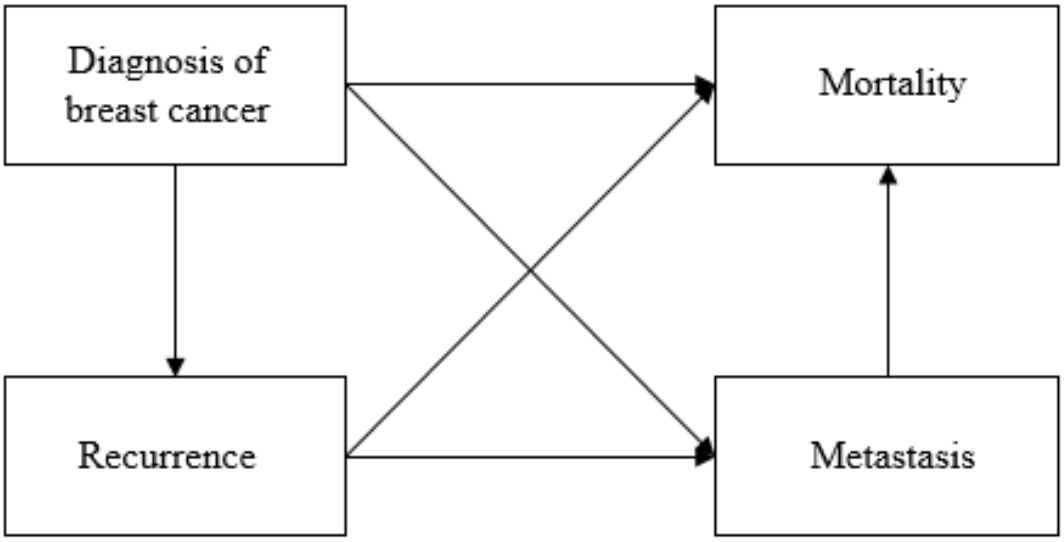

Fig. 1: The theoretical transitions of complications of breast cancer

In the state's breast cancer diagnosis, patients are biologically at risk of experiencing recurrence, metastasis and mortality simultaneously, and after recurrence they are biologically at risk of experiencing metastasis and mortality simultaneously in terms of competitive risks. The frequency of the observed transition between states from row to column in our sample is shown in Table 1. We specified the multistate models in which the transition intensity matrix is conducted by the Q matrix.

Table 1: Number of observed transitions between states (row and column) during study period in the breast cancer patients

Variables	*Total entering*	*Recurrence*	*Metastasis*	*Mortality*	*No event*
Diagnosis	2363	106	189	220	1848
recurrence	106	0	15	23	68
Metastasis	204	0	0	110	94
Mortality	353	0	0	0	353

$$Q = \begin{pmatrix} - & q_{12} & q_{13} & q_{14} \\ - & - & q_{23} & q_{24} \\ - & - & - & q_{34} \\ - & - & - & - \end{pmatrix}$$

In the Q matrix, q_{34} shows the transition from state 3 to state 4. By implementing the homogenous Markov multistate model, we estimated the Q matrix's transition intensity, which represents the instant risk of movement from state R to state S.

Due to specified Q matrix transitions in this model, there are six transitions which were numbered in the following order: (i) diagnosis to recurrence, (ii) diagnosis to metastasis, (iii) diagnosis to mortality (absorbing state), (iv) recurrence to metastasis, (v) recurrence to mortality and (vi) metastasis to mortality.

We examined different covariates to select the most effective independent variables for the final multistate analysis of the assumed model by interring them into the univariate multistate model alone once. We selected the variables which had a significant effect in at least one transition as influential variables for the final analysis. Finally, the variables age, lymph node, educational level, estrogen receptor status, and tumor size were selected as the desired risk factors of our final model.

The parametric continuous-time multistate model was used to estimate the effect of the study covariates on transitions between states (24). The transition hazard denotes the instantaneous risk of a subject's moving from one state of disease to another. It is determined by the current time and individual characteristics. The competing risks are considered by estimating cause-specific hazards (25). The data were analyzed using free R statistical software version 3.6.0. (mstate package).

Results

Our study's median (Q1-Q3) follow-up time was 5 (3-8) years. The mean (SD) of age at diagnosis of patients was 47.34 (10.98). 49.6% of patients had more than 12 years of education, and all the patients were female. The clinical baseline and demographic characteristics of the patients are reported in Table 2.

As shown in Table 3, the transition probability from diagnosis to recurrence was 4%. The probability of transition from recurrence to mortality was 0.21. The transition probability from metastasis to mortality was 53%.

Table 2: Demographic and clinical characteristics of breast cancer patients in total sample and event groups (recurrence, metastasis and, mortality) of breast cancer

Variables	***Total N(%)***	***Events rates***		
		Recurrence N(%)	Metastasis N(%)	Mortality N(%)
Age (yr)				
<50	1458 (61.7)	29 (5.8)	106 (7.3)	184 (12.6)
≥50	905 (38.3)	77 (4.1)	98 (10.8)	169 (18.7)
P-value*		*P*=0.102	*P*=0.003	*P*<0.001
Educational level				
< diploma	1191 (50.4)	48 (4)	130 (10.9)	217 (18.2)
≥ diploma	1172 (49.6)	58 (4.9)	74 (6.3)	136 (11.6)
P-value*		*P*=0.281	*P*<0.001	*P*<0.001
Lymph node				
No	931 (39.4)	47 (5)	49 (5.3)	76 (8.2)
Yes	1432 (60.6)	59 (4.1)	155 (10.8)	277 (19.3)
P-value*		*P*=0.309	*P*<0.001	*P*<0.001
Tumor size				
<2 cm	628 (26.6)	23 (3.7)	33 (5.3)	40 (6.4)
2-5 cm	1223 (51.8)	55 (4.5)	106 (8.7)	186 (15.2)
≥5	512 (21.7)	28 (5.5)	65 (12.7)	127 (24.8)
P-value*		*P*=0.342	*P*<0.001	*P*<0.001
Estrogen receptors				
Negative	497 (21)	29 (5.8)	61 (12.3)	93 (18.7)
Positive	1866 (79)	77 (4.1)	143 (7.7)	260 (13.9)
P-value*		*P*=0.102	*P*=0.001	*P*=0.008

**P*-value of Chi-square test comparing events in categories of variables

Table 3: Probability of next transition in baseline (model without covariate) model according to passing different times (years)

From	***To***	***Probability***
Diagnosis	Recurrence	0.04
Diagnosis	Metastasis	0.07
Diagnosis	Mortality	0.09
Diagnosis	No event	0.78
Recurrence	Metastasis	0.14
Recurrence	mortality	0.21
Recurrence	No event	0.64
Metastasis	mortality	0.53
Metastasis	No event	0.46

The current study determined the hazard ratio of the factors associated with breast cancer progression among patients. The effect coefficients of the elements in the model for each transition with their 95% confidence interval and significance can be seen in Table 4.

Table 4: Hazard ratio of breast cancer and its significant associated risk factors with complications in the different states of multistate models

Transition	***HR (95% CI)***				
	Age	Education	LN	ER	Tumor size
Diagnosis → Recurrence	0.99 (0.65, 1.49)	1.08 (0.72,1.60)	0.83 (0.55, 1.26)	0.76 (0.49,1.17)	1.46 (1.07,1.99)
P-value	*P*=0.966	*P*=0.702	*P*=0.395	*P*=0.215	*P*=0.014*
Diagnosis → Metastasis	1.58 (1.18, 2.12)	0.58 (0.43,0.79)	2.13 (1.50, 3.04)	0.65 (0.47,0.89)	1.46 (1.16,1.85)
P-value	*P*=0.002*	*P*<0.001*	*P*<0.001*	*P*=0.007*	*P*=0.001*
Diagnosis → Mortality	1.43 (1.08, 1.88)	0.61 (0.46,0.80)	2.06 (1.48, 2.86)	1.07 (0.77,1.48)	1.82 (1.46,2.27)
P-value	*P*=0.010*	*P*<0.001*	*P*<0.001*	*P*=0.658	*P*<0.001*
Recurrence → Metastasis	0.75 (0.24, 2.29)	0.51 (0.15,1.74)	1.29 (0.28, 5.83)	0.76 (0.23,2.47)	2.08 (0.84,5.09)
P-value	*P*=0.619	*P*=0.288	*P*=0.740	*P*=0.656	*P*=0.109
Recurrence → Mortality	1.75 (0.71, 4.34)	3.23 (1.19,5.72)	1.28 (0.44, 3.66)	0.44 (0.18,1.06)	2.69 (1.17,6.15)
P-value	*P*=0.221	*P*=0.120	*P*=0.643	*P*=0.067	*P*=0.018*
Metastasis →Mortality	1.35 (0.90, 2.03)	1.24 (0.71,1.91)	1.88 (1.02, 3.45)	0.69 (0.45,1.07)	1.67 (1.20,2.33)
P-value	*P*=0.140	*P*=0.314	*P*=0.040*	*P*=0.102	*P*=0.002*

*Statistical significant; HR, hazard ratio; CI, Confidence interval; LN, lymph node involvement; ER, Positive estrogen receptor

Based on the results in Table 4, patients over 50 years old had 58% more hazard of transition from diagnosis to metastasis and also 43% more hazard of transition from diagnosis to mortality compared to patients under 50 years old (*P*=0.002 and *P*=0.010, respectively). Having positive LN was significantly associated with a higher transition rate from diagnosis to metastasis by 2.13 times compared to patients with negative LN (*P*<0.001). Also, positive LN in comparison with negative LN significantly increased the hazard of transition from diagnosis to mortality and transition from metastasis to mortality by 2.06 times (*P*<0.001) and 1.88 times (*P*=0.040), respectively. Educational levels higher than high school significantly had a lower hazard of diagnosis to metastasis transition and diagnosis to mortality transition by 42% (*P*<0.001) and 39% (*P*<0.001), respectively.

Furthermore, the hazard ratio of transition from diagnosis to metastasis for patients with positive ER was 45% less than patients with negative estrogen receptors (*P*=0.007). One level increase in tumor size intensified the hazard of transitions from diagnosis to recurrence and transition from diagnosis to metastasis both by 46%, (*P*=0.014 and P=0.001) respectively. Also, one level increasing in tumor size increased the hazard of transition from diagnosis to mortality by 82% (*P*<0.001), the hazard of transition from recurrence to mortality by 2.69 times (*P*=0.018), and the hazard of transition from metastasis to mortality by 67% (*P*=0.002), respectively.

Fig. 2 indicates the cumulative hazard functions of each transition in the multistate model against time.

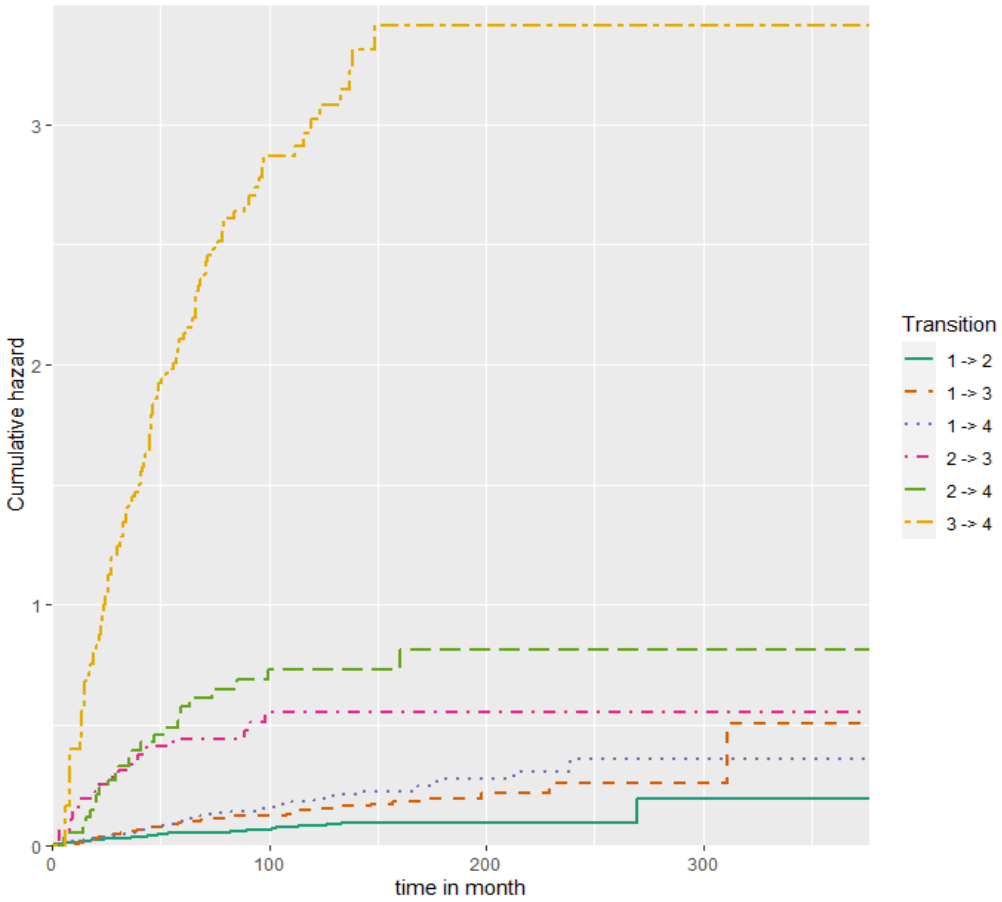

Fig. 2: Cumulative hazard functions for each transition in breast cancer complications in the multistate model (1→2 means cumulative hazard function for the transition from state 1 to state 2. States were numbered as state 1: diagnosis of breast cancer, state 2: recurrence, state 3: metastasis, and state 4: mortality.)

Discussion

This article aimed at estimating the prognostic factors correlated with the occurrence of types of breast cancer recurrence and mortality by multistate modeling. To achieve this goal, we presented a multistate model with a breast cancer diagnosis, two intermediate states (recurrence and metastasis), and mortality for model breast cancer states. We measured the effect of age, educational level, estrogen receptor status, lymph node status, and tumor size on the hazard ratio of transitions between breast cancer complications.

We found that hazard of metastasis occurrence after diagnosis over 50 years old increased 58% in comparison with ages under 50 years old significantly and also hazard of mortality after diagnosis (without experiencing recurrence and metastasis) over 50 years old increased 43% in comparison with ages under 50 years old significantly (by HR= 1.58 and HR=1.43, respectively).

Consistent with the results of our study, several studies have shown that aging is negatively related to the survival of breast cancer patients (26) and accelerated the development of breast cancer complications as metastasis (27, 28). One unit increase of age in breast cancer patients increased 1.02 the mortality ratio (29). Even though evidence has introduced the lower age as a poor prognostic factor in breast cancer patients' survival (30, 31), it may be due to different frequencies of the studied population. Sub-group analysis in different age strata may provide more convincing evidence.

We found that positive LN increased the hazard of metastasis occurrence after breast cancer diagnosis by 2.13 times compared to negative LN. As well as, it increased the transition hazard from diagnosis to mortality and transition from metastasis to mortality in the amount of 2.06 times and 1.88 times, respectively. This finding is in line with the results of previous studies, which reported positive LN as a risk factor for risk of metastasis (32) and mortality (33) after diagnosis of breast cancer. It may insist on the importance of early detection strategies to find breast cancer in lower stages without LN involvement.

According to our results, patients with diploma and college education educational level had lower risk of transition from diagnosis to metastasis up to 42% and the hazard of transition from diagnosis to mortality up to 39% compared to diploma and lower educational level ($P<0.001$). Women with higher educational levels may notice the symptoms of their disease in primary stages, which can receive more effective treatment. Therefore the chances of metastasis occurrence are lower in higher educational levels (34, 35). Considering shorter follow-up intervals in persons with lower educational levels may help provide a better prognosis for them.

Our results show that having positive ER compared with negative ER was negatively related to the hazard ratio of metastasis occurrence after diagnosis of breast cancer by hazard ratio 65%. Yip et al. showed that patients with positive estrogen receptors had longer disease-free intervals and experienced no breast cancer recurrence later than patients with negative estrogen receptors (36). Positive ER has an important role in the metastatic process in breast cancer patients (37). Because of this correlation, estrogen receptor status has been an important factor in a breast cancer treatment protocol.

Our findings showed that tumor size had a positive role in increasing the hazard of transitions from diagnosis to recurrence, diagnosis to metastasis, and diagnosis to mortality by 1.46, 1.46, and 1.82 times in breast cancer patients, respectively. Furthermore, it increased the hazard of transition from recurrence to mortality and metastasis to mortality by 2.69 and 1.67 times per level of increase in tumor size, respectively. This correlation has been approved in previous studies (38, 39). A survey of the association of tumor size and metastasis indicated that the capacity for a primary breast tumor to metastasis increases as cancer progresses (40). Another study has shown that tumor size is positively related to recurrence in breast cancer patients (41).

Providing educational and informational programs for women in the field of early diagnosis of breast cancer may be helpful for increasing the chance of survival and improving their quality of life. This model may provide more valuable insight by using more critical risk factors for future researches. Limitations of this study include a small number of events in some transitions and incomplete information about some patients participating in the study that should be considered.

Conclusion

The effect of prognostic factors of breast cancer was investigated on the risk of intermediate events of breast cancer along with mortality by the multistate model. This model provided a flexible framework to study and compare the effects and estimate the prediction of intended prognostic factors simultaneously on breast cancer states.

Multistate model presented the detailed effects of prognostic factors on middle states of breast cancer and mortality. Implementing early diagnosis strategies and providing informational programs, especially in younger ages and lower educational level patients may be helpful in reducing the hazard of transition to higher states of breast cancer and increasing the survival of Iranian women with breast cancer by controlling tumor size growth, lymph nodes involvements and estrogen receptor status.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare no conflicts of interest.

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