Original Article
Middle East Journal of Cancer; January 2022; 13(1): 150-158

The Effects of Prognostic Factors on Metastasis and Survival of Patients with Breast Cancer Using a Multi-State Model

Ebrahim Babaee*, PhD, Nahid Nafissi, MD, Arash Tehrani-Banihashemi*, PhD, Babak Eshrati*, MD, MPH, PhD, Leila Janani*, PhD, Marzieh Nojomi*,***♦, MD, MPH**

**Preventive Medicine and Public Health Research Center, Psychosocial Health Research Institute, Community and Family Medicine Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
***Breast Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*
****Department of Sociology and Anthropology, Nipissing University, North Bay, Ontario, Canada*

Please cite this article as: Babaee E, Nafissi N, Tehrani-Banihashemi A, Eshrati B, Janani L, Nojomi M. The effects of prognostic factors on metastasis and survival of patients with breast cancer using a multi-state model. Middle East J Cancer. 2022;13(1):150-8. doi: 10.30476/mejc.2021.89311.1519.

♦Corresponding Author:
Marzieh Nojomi, MD, MPH
Preventive Medicine and Public Health Research Center, Psychosocial Health Research Institute, Department of Community and Family Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
Email: mnojomi@iums.ac.ir

Abstract

Background: The multi-state models help more closely study of the factors affecting the survival of patients with breast cancer.

Method: We conducted the present retrospective cohort study on 2030 Iranian patients with breast cancer in 2020. The patients' follow-up period ranged from 1 month to 15 years. Accordingly, the initial treatment, metastasis, and death were considered as the first, second, and absorbing states, respectively. The multi-state model was utilized for modeling and analyzing the data at a 95% significance level using the MSM package in R software.

Results: The mean age (± standard deviation) of the patients included at diagnosis time was 55.3 (±12.07) years old. The first one year and 5 years adjusted transition probabilities for transitions from the treatment to metastasis estimated as 0.85 (0.15 – 0.89) and 0.45 (0.21 – 0.61), and for metastasis to death transitions, they were estimated as 0.15 (0.1 – 0.21) and 0.55 (0.41 - 0.69), respectively. Moreover, the average sojourn times were estimated as 0.27 and 74.85 months for the treatment and metastasis states, respectively.

Conclusion: The obtained results revealed that over time, the transition probabilities of patients from surgery to metastasis state decreased, whereas the transition probabilities from metastasis to death state increased using the multi-state model.

Keywords: Multi-state model, Prognostic factors, Survival analysis, Breast cancer

Introduction

In most countries worldwide, different types of cancer are considered as the most important health threat after non-communicable diseases. The World Health Organization reported that cancer is the first or second leading cause of

Received: December 16, 2020; Accepted: February 21, 2021

Table 1. Metastasis and death status of breast cancer patients based on the clinical and pathological characteristics (n= 2030)

Variables	Number[a] (%)	Metastasis (N, %)	*P* value	Death (N, %)	*P* - value
Age group (yr)					
< 30	12 (0.6)	3 (1.8)		1 (1.1)	
30-39	170 (8.5)	18 (11.2)		9 (9.5)	
40-49	466 (22.9)	36 (22.4)		19 (20)	
50-59	680 (33.5)	62 (38.5)		41 (43.2)	
60-69	426 (20.9)	29 (18)		17 (17.8)	
≥70	276 (13.6)	13 (8.1)	0.029	8 (8.4)	0.299
Radiotherapy type					
IORT[b]	605 (33.5)	25 (16.7)		6 (6.8)	
EBRT[c]	1200 (66.5)	125 (83.3)	< 0.001	82 (93.2)	< 0.001
Estrogen receptor					
Positive	1332 (72.6)	96 (61.5)		54 (58.7)	
Negative	502 (27.4)	60 (38.5)	< 0.001	38 (41.3)	0.002
Progesterone receptor					
Positive	1283 (69.9)	95 (60.9)		53 (5.6)	
Negative	552 (30.1)	61 (39.1)	0.01	39 (42.4)	0.008
HER2[d]					
Negative	1234 (82.7)	89 (75.4)		58 (75.3)	
Positive	258 (17.3)	29 (24.6) 0.029		19 (24.7)	0.079
Tumor grade					
I	181 (9.8)	7 (4.8)		4 (4.5)	
II	971 (52.5)	61 (41.8)		32 (36.4)	
III	697 (37.7)	78 (53.4)	< 0.001	52 (59.1)	< 0.001
Stage at diagnosis					
I	459 (24.5)	18 (12.5)		9 (10.2)	
II	943 (50.4)	57 (39.6)		33 (37.5)	
III	450 (24.1)	60 (41.7)		41 (46.6)	
IV	18 (1)	9 (6.2)	< 0.001	5 (5.7)	< 0.001

[a]The sum of subgroups may be less than total because of missing data; [b]Intraoperative radiation therapy; [c]External beam radiation therapy; [d]Human epidermal growth factor receptor 2

death in most countries.[1] Correspondingly, breast cancer is the most prevalent cancer worldwide, accounting for 1.4% of all the cancers and 29% of those in women.[2, 3] It is noteworthy that breast cancer mortality rate is lower in Asian countries, such as China and Japan, compared with European countries and America.[4] This cancer is also the most common malignancy among women in Iran.[5] Unfortunately, in Iran, breast cancer is mostly diagnosed in women at advanced stages.[6] A study performed in 2018 showed that the epidemiology and histopathology of breast cancer in Iranian patients differed from those of the neighboring countries.[7] The re-appearance of breast cancer at any site is defined as recurrence, which is also categorized as distant (metastasis) or local recurrence.[8] Accordingly, it could be said that metastasis is the main factor in reducing the survival of patients with breast cancer.[9] Death and metastasis are interesting outcomes that researchers mostly consider in survival analysis of cancer-associated data.[10]

In most non-communicable patients, particularly those with cancer, multiple states and transitions are predictable. In breast cancer, surgery or initial treatment, metastasis, and death may be considered as known states and the patient's movement among these states is considered as possible transition.[10,11]

In diseases like cancers with multiple endpoints, the multi-state models work appropriately and efficiently in the analysis and assessment of the states and transitions.[12] Among several methods used to identify the factors affecting the survival of patients with breast cancer, the above-mentioned models are known to be appropriate and very effective.[13] In addition, these methods help in studying the factors affecting the survival time of patients more closely, by considering the intermediate cases and investigating the effects of the covariates for each transition.[14] The multi-state analysis model is one

Table 2. Transition matrix of breast cancer patients based on the states of disease

Condition	Initial Treatment (State I)	Metastasis (State II)	Death (State III)
Initial Treatment (State I)	3738	161	0
Metastasis (State II)	0	66	95
Death (State III)	0	0	0

of the suitable methods for analyzing such data with consecutive events.[15] Finally, the results of these analysis models have provided valuable clinical information.

In this study, we used the multi-state model to analyze the obtained data related to breast cancer. This study aimed to determine the survival rate and measure the effects of the factors on the progression of the breast cancer from the surgery state to the interested endpoints, such as metastasis and death, considering transmission paths.

Methods

This registry-based retrospective cohort study was conducted in 2020, on 2030 Iranian patients with breast cancer referred to Rasool-E-Akram (PBUH) Hospital, affiliated with Iran University of Medical Sciences between 2000 and 2019. The Research Council of Iran University of Medical Sciences approved the present study (No.: 13626). The cases were referred to this center from hospitals, laboratories, and other medical facilities in Tehran as well as some other provinces. The data were obtained from the patients' electronic medical records using a checklist and considering the demographic data (age), clinical features, surgery type, history of metastasis, adjuvant treatments (chemotherapy and radiotherapy), and dates of surgery, metastasis, and the last follow-up.

In addition to the surgery, all the patients underwent at least one other treatment, such as chemotherapy, hormone therapy, and radiotherapy. In the analysis, this process was considered as the initial treatment state. Notably, the included patients were candidates for intraoperative radiation therapy (IORT) or external whole-breast irradiation (EBRT) based on their clinical and pathological statuses, who were then selected for partial breast irradiation in terms of the recent guidelines published by the American Society for Radiation Oncology.[16]

The patients' follow-up time ranged from 1 month to 15 years. The subjects with incomplete records, pregnancy, lactation, or cancer other than breast cancer on top of those who died due to some reasons other than breast cancer or could not complete the follow-up were excluded from this study.

Due to the normal course of breast cancer, people may experience metastasis after surgery and then die with or without experiencing

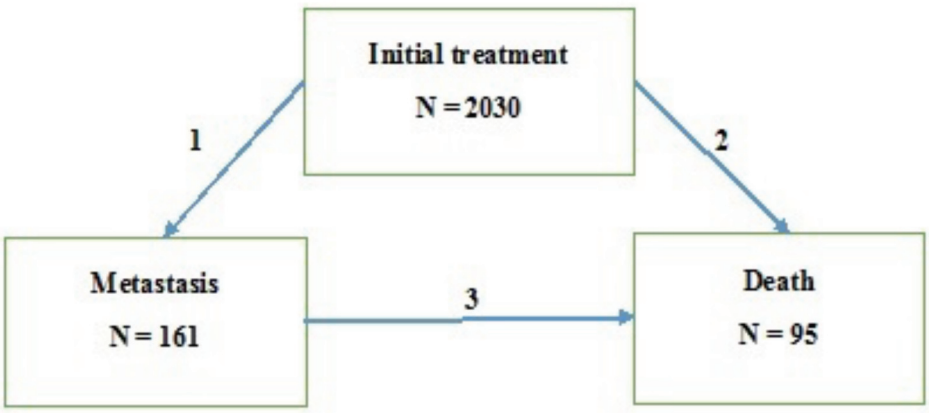

Figure 1. Breast cancer disease transition paths estimated using multistate model.

Table 3. The 5-year transition probabilities matrix in breast cancer patients

Variables	Transition Paths	Non-adjusted Probability	95% CI[a]	*P* Value	Adjusted[b] Probability	95% CI	*P* Value
12 months	Surgery →Metastasis	0.83	(0.79 – 0.85)	< 0.05	0.85	(0.15 – 0.89)	< 0.05
	Metastasis →Death	0.17	(0.14 – 0.21)	< 0.05	0.15	(0.1 – 0.21)	< 0.05
24 months	Surgery→Metastasis	0.68	(0.63 – 0.73)	< 0.05	0.73	(0.12 – 0.81)	< 0.05
	Metastasis →Death	0.3	(0.26 – 037)	< 0.05	0.27	(0.19 – 0.38)	< 0.05
36 months	Surgery →Metastasis	0.56	(0.51 – 0.63)	< 0.05	0.62	(0.16 – 0.72)	< 0.05
	Metastasis →Death	0.4	(0.36 – 0.49)	< 0.05	0.3	(0.28 – 0.52)	< 0.05
48 months	Surgery→Metastasis	0.47	(0.39 – 0.53)	< 0.05	0.53	(0.19 – 0.67)	< 0.05
	Metastasis→Death	0.5	(0.46 – 0.6)	< 0.05	0.47	(0.34 – 0.61)	< 0.05
60 months	Surgery →Metastasis	0.39	(0.32 – 0.47)	< 0.05	0.45	(0.21 – 0.61)	< 0.05
	Metastasis →Death	0.61	(0.53 – 0.68)	< 0.05	0.55	(0.41 – 0.69)	< 0.05

[a]Confidence interval; [b]Adjusted for all variables listed in Table1

metastasis until the end of the follow-up period. Therefore, three states were considered in this study as follows: the initial treatment, metastasis, and death as the first, second, and absorbing states, respectively. Based on the multi-state model, each subject would experience at least one of the above-mentioned states with a transitional probability after surgery as the first state. Finally, the transition paths included surgery to metastasis, metastasis to death, and surgery to death. Herein, death was the absorbing state and there is no other state after the absorbing state.[11] It should be noted that due to the nature of breast cancer disease, the reversal transitions were not considered in the model. Figure 1 represents the considered states and transition paths for the multi-state model.

In the present study, the multi-state model was utilized for modeling and analyzing the obtained data.[17,18] Based on the initial transition density and matrix, the initial rough values were estimated for transition intensities. Thereafter, we applied the maximum likelihood approach to estimate the parameters of Markov continuous-time model; the data were then fitted based on this model. Subsequently, in order to estimate the effects of the independent variable on the transition hazards, we calculated hazard ratios using univariate Cox proportional hazard regression models, including a time-dependent covariate. To avoid estimation biases, the multiple approaches were applied to estimate the adjusted hazard ratios. Afterwards, the Ellen Johnson estimator was employed for estimating the transition probabilities. The demographical and clinical characteristics, such as age at the diagnosis time, radiotherapy types (EBRT, IORT), estrogen receptor status (ER-, ER+), progesterone receptor status (PR-, PR+), human epidermal growth factor receptor 2 status (HER2+, HER2-), tumor grade (I. II, III), and stage at the diagnosis time (I, II, III, IV) were considered as predictive covariates of metastasis and death, which were then tested for each transition (Table1).

The proportional hazards' assumption was justified using the Schoenfeld residuals test. Next, each variable was primarily tested in univariate analysis. Using the stepwise selection model, those factors that were significantly associated with the considered states were then selected to perform multivariate analysis. The sojourn time was also estimated in each state. To summarize the quantitative and categorical variables, mean (± standard deviation (SD)) and frequency (percentage) were used, respectively. For note, all the statistical analyses were performed at a 95% significance level utilizing the MSM package in R software version 4.0.2.

Results

Based on the inclusion and exclusion criteria, a total of 2030 patients with confirmed breast cancer participated in this study. The mean age (±SD) of the patients at the time of diagnosis was 55.3 (±12.07) years old and their age range was from 22 to 95 years old. Most of the patients (33.5) were in the age group of between 50 and 59 years old. The percentages of ER+, PR+, and

Table 4. Prognostic factors for each transition with hazard ratios and their 95% confidence intervals in multiple analyses

Variables	Transition Paths	Hazard Ratio	95% CI	*P* Value
Age at diagnosis	Surgery →Metastasis	1.01	(0.66 - 1.54)	> 0.05
	Metastasis →Death	0.99	(0.97 - 1.02)	> 0.05
Radiotherapy type	Surgery →Metastasis	7.39	(0.19 - 28.74)	> 0.05
(EBRT vs.[a] IORT)	Metastasis →Death	1.37	(0.57 - 3.29)	> 0.05
Estrogen receptor	Surgery →Metastasis	1.07	(0.58 - 4.45)	> 0.05
(ER[b] vs. ER[c])	Metastasis →Death	0.88	(0.72 - 2.08)	> 0.05
Progestogen receptor	Surgery →Metastasis	0.95	(0.63 - 3.42)	> 0.05
(PR+ vs. PR-)	Metastasis →Death	0.58	(0.49 - 1.34)	> 0.05
HER2	Surgery →Metastasis	0.49	(0.19 - 16.35)	> 0.05
(HER2+ vs. HER2-)	Metastasis →Death	0.84	(0.61 - 1.15)	> 0.05
Tumor grade	Surgery →Metastasis	6.48	(0.55 - 28.39)	> 0.05
(II-III vs. I)	Metastasis →Death	1.12	(0.83 - 1.51)	> 0.05
Stage at diagnosis	Surgery →Metastasis	1.14	(0.66 - 20.88)	> 0.05
(II-III-IV vs. I)	Metastasis →Death	1.13	(0.79 - 1.63)	> 0.05

[a]Versus ; [b]Estrogen receptor; [c]Progesterone receptor; EBRT: External whole-breast irradiation; IORT: Intraoperative radiation therapy; HER2: Human epidermal growth factor receptor 2

HER2– in these patients were 72.6%, 69.9%, and 82.7%, respectively. Moreover, the IDC cancer was the most common (77%) type among them. Metastasis and death were also reported in 7.9% (n=161) and 4.7% (n=95) of the patients, respectively. Most patients were at stage II (50.4%) and had grade II (52.5%) cancer at the diagnosis time. Table1 shows the metastasis and death statuses of the subjects based on their clinical and pathological characteristics. In this study, the median follow-up time was 32.1 months (range, 1-201 months).

No death occurred in the initial treatment state; however, 161 metastases occurred at this stage and 95 deaths occurred in the metastasis state (Table 2). Due to the nature of breast cancer, the reversal transitions, for instance death, to metastasis and metastasis to the initial treatment state were impossible; thus, we observed no specific events in these paths.

The 5-year adjusted and non-adjusted transition probabilities matrix with 1-year intervals was calculated with Markov multi-state model (Table 3). Based on the non-adjusted approach, the first 1-year transition probabilities for transitions from the initial treatment to metastasis and metastasis to death states were calculated as 0.83 (0.79 – 0.85) and 0.17 (0.14 – 0.21), respectively. Furthermore, 5-year transition probabilities from the initial treatment to metastasis and metastasis to death states were estimated to be 0.39 (0.32 – 0.47) and 0.61 (0.53 – 0.68), respectively. Additionally, the first 1-year adjusted transition probabilities for transitions from the initial treatment to metastasis and metastasis to death states were calculated to be 0.85 (0.15 – 0.89) and 0.15 (0.1 – 0.21) and for 5-year adjusted transition probabilities for the above-mentioned transitions; they were estimated as 0.45 (0.21 – 0.61) and 0.55 (0.41 - 0.69), respectively.

Once fitting the multi-state model with independent variables compared to the model without independent variables significantly justified to the data, the Markov multi-state model was fitted to the obtained data and the adjusted hazard ratios of transitions were then estimated using multivariate multi-state analysis model (Table 4). As reported earlier, with the increase in age at the diagnosis time, there were no considerable effects on breast cancer metastasis in the patients in the initial treatment state hazard ratio (HR): 1.01, (0.66 - 1.54)] and death of those in the metastasis state [HR: 0.99, (0.97 - 1.02)]. Regarding the radiotherapy methods, the EBRT method increased the hazard of transition from the initial treatment state to the metastasis state in comparison with the IORT method [HR: 7.39, (0.19 – 28.74)] and transition from the metastasis state to the death state [HR: 1.37, (0.57 - 3.29)]. In the following, the stage at the diagnosis time greater than or equal to II [HR: 1.14, (0.66 - 20.88)] and tumor grade greater than or equal to

Table 5. The estimated mean sojourn time (in months) using the multi-state model

Condition	Estimates	SE	95% CI
Initial treatment	0.27	0.88	(0.49 – 1.53)
Metastasis	74.85	15.48	(49.9 – 112.27)

SE: Standard error; CI: Confidence interval

II [HR: 6.48, (0.55 - 28.39)] were found to have an increased hazard on distant metastasis. Moreover, it was observed that the stage at the diagnosis time greater than or equal to II [HR: 1.13, (0.79 - 1.63)] and the tumor grade greater than or equal to II [HR: 1.12, (0.83 - 1.51)] had an increased hazard on death following metastasis. Table 4 depicts the effects of some other variables on transition hazards. The average sojourn times of the patients with breast cancer in the initial treatment and metastasis states were estimated to be 0.27 and 74.85 months, respectively (Table 5).

Discussion

In the present study, we investigated the effect of certain important clinical characteristics of the included patients, such as tumor grade, stage of cancer at diagnosis, ER status, PR status, HER2 status, and radiotherapy methods (IORT, EBRT) on their transitions and placement probability in the disease states using the multi-state models.

In our study, three states were considered as follows: initial treatment, metastasis, and death as the first, second, and absorbing states, respectively. About 161 metastases occurred in the initial treatment state and 95 patients were transferred from metastasis state to the death state. In addition, no breast cancer patients were directly transferred to the death state with no metastasis following the initial treatment state.

Based on our findings, the increase in age did not significantly affect the incidence of metastasis and death of patients experiencing metastasis, which is consistent with the results of other studies.[11,14,19] In a study by De Bock et al. using the multi-state method, increased age was found to be associated with the increased distant metastasis.[20] However, a similar previous study showed that the increase in age can be effective on directly transferring patients from surgery to death.[21] Furthermore, in certain studies, the survival of breast cancer patients was observed to be inversely related to age, as one study showed that developing breast cancer at older ages reduces the survival of the patients.[22]

Our obtained results also revealed that after adjustment for other variables, the PR+, ER+, and HER2+ variables were not associated with the increased hazard of death of breast cancer patients; therefore, they could be defined as protective factors. In addition, ER+ status increased the risk of metastasis by about 7% after the initial treatment and the PR+ and HER2+ status decreased the risk of metastasis by about 5% and 51% after the initial treatment state. In this regard, it should be noted that our findings are not consistent with the results of a previous study performed in 2018;[12] however, findings of several other studies confirmed ours.[14,19,23]

Some recent studies have investigated the impacts of local and distant metastasis on survival on the patients with breast cancer with time-dependent covariates using a Cox regression model.[24] However, only few studies with multi-state models have examined the effect of different variables on disease transmission.

In this regard, the multi-state models could provide some useful information on transmissions among the states of the disease as well as the effects of various factors on the development of such transmissions.[25]

In the present study, we showed that the EBRT method compared with the IORT method, a stage greater than or equal to stage II in comparison with stage I, and a tumor grade greater than or equal to grade II compared with tumor grade I were attributed to the increased hazard on transitions from treatment to metastasis and from metastasis to death state. However, the estimated results in this regard were not significant. The results of several previous studies confirmed our findings reporting that the advanced tumor grade

and stage at the diagnosis time had a significantly increased risk on the transition to death and metastasis.[17,20,26] None of the reviewed studies has examined the effects of different types of radiotherapy on the outcomes of breast cancer with the multi-state model.

The multi-state models could also provide useful information on the progression of different states of the disease and the probability placement of a certain number of patients in the states of the disease.[27]

Herein, considering the effect of the above-mentioned clinical and pathological characteristics of the patients, we also calculated the probability of transitions among the states of events for the patients at 1 to 5 years and those with 1-year intervals. We indicated these probabilities as two adjusted and non-adjusted modes, separately. As estimated, the adjusted transition probability showed that in the first year, the probabilities of transition of the patients from the initial treatment to metastasis state and from metastasis state to death state were 85% and 15%, respectively. Based on the results, the probability of metastasis after the initial treatment decreased with the follow-up time and the probability of death in the patients also increased after the metastasis. Subsequently, after 5 years, the estimated probabilities for transitions from the initial treatment state to metastasis and metastasis to death state reached 45% and 55%, respectively.

Sojourn time is considered as another measurement in these models of analysis. This measurement determines the average durability of patients at each state considering the effect of independent variables related to each state. Based on our findings, the maximum estimated mean sojourn times for the treatment and metastasis states were 0.27 and 75 months, respectively.

It should be noted that although multi-state methods provide valuable information on the nature of diseases, these analysis models have certain limitations; for example, it seems that they are not able to provide a proper description of the biological process of the disease. Additionally, in diseases with multiple simultaneous transition pathways, utilizing the multi-state models may be difficult or impossible.[17]

The authors acknowledged that this study has some potential limitations and further complementary measures are required. Primarily, due to low transition numbers, the statistical power of our analysis model may be lower than that of other studies with multiple transitions and with the same design. Secondly, in our data, some states like metastasis were considered in a binary mode, while the patients may have multiple metastases' history and the multiplicity of metastases could have an increasing effect on the occurrence of death as the next stage. In addition, in this study, the selection bias should be considered due to the excluded incomplete patient records. Nevertheless, the number of excluded patients was not significant in this regard. Despite these shortcomings, multi-state models can provide more useful information on the nature of diseases like breast cancer compared with the other survival models. Furthermore, we believe that our research, with a relatively large sample size and almost different results, along with the findings of other studies could be valuable and applicable for future investigations.

Conclusion

In the current study, we estimated the HRs and transition probabilities of transitions using a multi-state model. Although interpreting the results of the studies extracted from multi-state models was not clinically easy, these models provided valuable information in terms of disease outcomes and transition paths formation for clinical usage. In this study, we indicated the transition paths of breast cancer. The results of our study showed that over time, the transition probabilities of patients decreased. Meanwhile, the results of the transition probabilities from metastasis to death state were opposed to those from surgery to metastasis state. Our findings also revealed that the EBRT method, advanced stage, and grade of the tumor increased the hazard of transition from the surgery state to the metastasis state.

Acknowledgments

The authors would like to express their appreciation to the Vice-Chancellor of Research and Technology at Iran University of Medical Sciences for supporting this work.

Conflict of Interest

None declared.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65(2):87-108. doi: 10.3322/caac.21262.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34. doi: 10.3322/caac.21551.
3. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. *JAMA Oncol.* 2019;5(12):1749-68. doi: 10.1001/jamaoncol.2019.2996.
4. DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. *CA Cancer J Clin.* 2019;69(3):211-33. doi: 10.3322/caac.21555.
5. Roshandel G, Ghanbari-Motlagh A, Partovipour E, Salavati F, Hasanpour-Heidari S, Mohammadi G, et al. Cancer incidence in Iran in 2014: results of the Iranian National Population-based Cancer Registry. *Cancer Epidemiol.* 2019;61:50-8. doi.org/10.1016/j.canep.2019.05.009.
6. Shahkhodabandeh S, Piri Z, Biglo M, Asadi M, Chakhmachi DN. Breast cancer in Iran: Iranian scientists approach to breast cancer researchers in Medline database. [In Persian] *Iran J Breast Dis.* 2009;2(2): 49-59.
7. Nafissi N, Khayamzadeh M, Zeinali Z, Pazooki D, Hosseini M, Akbari ME. Epidemiology and histopathology of breast cancer in iran versus other middle eastern countries. *Middle East J Cancer.* 2018;9(3):243-51. doi.10.30476/MEJC.2018.42130.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687-717. doi: 10.1016/S0140-6736(05)66544-0.
9. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol.* 1996;14(10):2738-46. doi: 10.1200/JCO.1996.14.10.2738.
10. Mazroui Y, Mathoulin-Pélissier S, Macgrogan G, Brouste V, Rondeau V. Multivariate frailty models for two types of recurrent events with a dependent terminal event: application to breast cancer data. *Biom J.* 2013;55(6):866-84. doi: 10.1002/bimj.201200196.
11. Putter H, van der Hage J, de Bock GH, Elgalta R, van de Velde CJ. Estimation and prediction in a multi-state model for breast cancer. *Biom J.* 2006;48(3):366-80. doi: 10.1002/bimj.200510218.
12. Grover G, Swain PK, Goel K, Singh V. Multistate Markov modelling for disease progression of breast cancer patients based on CA15-3 marker. *Thailand Statistician.* 2018;16(2):129-39.
13. Hosseni AF, Gohari MR. Application of multilevel model in determining the effective factors in the length of stay among appendectomy patients. [In Persian] *Razi Journal of Medical Sciences (RJMS).* 2014;20(115):70-7.
14. Raesizadeh M, Seghatoleslami M, Hoseinzade M, Saki Malehi A. Survival analysis of breast cancer patients according to intermediate and endpoint events: Applying illness-death model. [In Persian] *The Iranian Journal of Epidemiology (IJE).* 2018;13(4):291-8.
15. Amirkafi M. The significance and logic of multilevel models in social research. [In Persian] *Iranian J of Sociology.* 2007;7(4):38-71.
16. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated partial breast irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. *Pract Radiat Oncol.* 2017;7(2):73-9. doi: 10.1016/j.prro.2016.09.007.
17. Broët P, de la Rochefordière A, Scholl SM, Fourquet A, De Rycke Y, Pouillart P, et al. Analyzing prognostic factors in breast cancer using a multistate model. *Breast Cancer Res Treat.* 1999;54(1):83-9. doi: 10.1023/a:1006197524405.
18. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med.* 2007;26(11):2389-430. doi: 10.1002/sim.2712.
19. Faradmal J, Mafi M, Sadighi-Pashaki A, Karami M, Roshanaei G. Factors affecting survival in breast cancer patients referred to the darol aitam-e mahdieh center. [In Persian] *J Adv Med Biomed Res.* 2014;22(93):105-15.
20. De Bock G, Putter H, Bonnema J, Van Der Hage J, Bartelink H, Van De Velde C. The impact of loco-regional recurrences on metastatic progression in early-stage breast cancer: a multistate model. *Breast Cancer Res Treat.* 2009;117(2):401-8. doi: 10.1007/s10549-008-0300-2.
21. Hajihosseini M, Faradmal J, Sadighi-Pashaki A. Survival analysis of breast cancer patients after surgery with an intermediate event: application of illness-

death model. *Iran J Public Health*. 2015;44(12):1677.
22. Lakzaei M, Salarilak S, Khalkhali HR, Maleki D, Esnaashari O. Association between age of morbidity and prognosis of breast cancer. [In Persian] *Studies in Medical Sciences.* 2015;26(7):625-33.
23. Moghadami FZ, Abolghasemi J, Asgari DA, Gohari M. Survival analysis of patients with breast cancer using the Aalen's additive hazard model. [In Persian] *Journal of North Khorasan University of Medical Sciences (NKUMS)*. 2011;3:171-80. doi: 10.29252/jnkums.3.5.s5.171.
24. Haffty BG, Reiss M, Beinfield M, Fischer D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. *J Clin Oncol.* 1996;14(1):52-7. doi: 10.1200/JCO.1996.14.1.52.
25. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Softw.* 2011;38(8):1-29. doi: 10.18637/jss.v038.i08.
26. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet.* 1991;338(8763):327-31. doi: 10.1016/0140-6736(91)90475-5.
27. Saint-Pierre P, Combescure C, Daurès JP, Godard P. The analysis of asthma control under a Markov assumption with use of covariates. *Stat Med*. 2003;22(24):3755-70. doi: 10.1002/sim.1680.