Risk of multiple primary tumors in breast cancer survivors

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Abstract. This study aimed to investigate the risk factors associated with subsequent multiple primary tumors in female breast cancer survivors by using analytical method for recurrent data. A total of 389,344 patients with primary breast cancer were enrolled from the SEER (Surveillance, Epidemiology, and End Results) database. The outcome of this study was the diagnosis of multiple primary tumors. SEER rules were used to define the multiple primary tumors. The comparison between the data of each group was performed by χ² test. Risk factors of multiple primary tumors were examined by marginal means and rates model. A total of 42020 (10.79%) patients developed multiple primary cancers, of which the majority of patients (38,767, 92.3%) with second primary tumor. There were 3013 cases and 240 cases of third primary tumor and fourth primary tumor, respectively. Older age, black race, large tumor size (> 2 cm), negative HR, mixed initial tumor histology, poor differentiated or differentiated cancer cells, and lumpectomy were associated with higher risk of subsequent multiple primary tumors. More active clinical monitoring and follow-up should be performed on breast cancer survivors who are at higher risk of multiple primary tumors, thereby improving their prognosis and life quality.

1. Introduction
In the United States, breast cancer is the most common cancer among women of all races. According to the report of American Cancer Society, the incidence of breast cancer in women increased at a rate of 0.4% per year from 2006 to 2015. By 2016, more than 3.5 million women had been diagnosed with invasive breast cancer [1]. Unlike high morbidity rates, female breast cancer mortality had fallen by 40% from 1989 to 2016 [2], which is related to advances in technology of breast cancer diagnosis and treatment. As the number of breast cancer patients increased, poor prognosis of breast cancer has become a new public health problem, such as the occurrence of multiple primary cancers. Previous studies have shown that breast cancer patients have a higher risk of subsequent multiple primary cancers than the general population [3-5], especially during the first decade after diagnosis [3]. The high risk of multiple primary cancers is reported to be related to age [6], ethnicity or race [7], cancer treatment side effects [8], carcinogenic environmental factors [9], and lifestyle.

Previous studies have focused on the risk and risk factors of second primary cancer. However, primary breast cancer patients may develop subsequent multiple primary tumors during follow-up
period. If only one primary tumor occurrence is chosen as the outcome, the data information is underutilized and the effect of the risk factor cannot be accurately evaluated. When the interested event occurs more than once, the traditional Cox proportional hazard model, which is only applicable to survival data with single outcome, cannot be used for the analysis of recurrent data. This study aimed to investigate the risk factors associated with subsequent multiple primary tumors in female breast cancer survivors by using analytical method for recurrent data.

2. Materials and methods

2.1. Data source and study population
Data was derived from SEER (Surveillance, Epidemiology, and End Results) database (2018 version). Since 1973, the SEER project has collected information on breast cancer patients in various regions of the United States, including patients’ demographic characteristics, clinical pathological features of tumor and treatments [10].

The criteria for inclusion in this study are as follows: 1) Women with a primary breast cancer diagnosis between the age of 20 and 80; 2) The primary breast cancer diagnosis was diagnosed before the end of 2011 to ensure that each patient had at least 5 years of follow-up. Exclusion criteria includes: 1) Data was collected from the report of death or autopsy; 2) There were missing values in demographic or clinical pathological variables. In total, 389,344 primary breast cancer patients were included in the study, and all information was collected from year of 1998 to 2016.

2.2. Outcome and covariates
The outcome of the study was the diagnosis of multiple primary tumors. SEER rules were used to define the multiple primary tumors. The SEER definition takes into account the tumor site, tumor stage, type of tumor histology, the interval between two diagnoses, and the laterality in paired organs [11]. The demographic characteristics included age at initial diagnosis and ethnicity (White, Black, and Asian/Pacific Islander). Tumor characteristics included laterality, tumor size, lymph node status, hormone receptor (HR) status (positive: either estrogen receptor or progesterone receptor was positive; negative: both estrogen and progesterone receptor were negative.), histological type, tumor grade, and tumor stage. The treatment information only included surgical type.

2.3. Statistical analyses
The patient characteristics were grouped and described according to whether the patient had an occurrence of subsequent primary tumors as well as the order of multiple primary tumors. The comparison between the data of each group was performed by χ2 test. P < 0.05 was considered statistically significant. Risk factors of multiple primary tumors were examined by marginal means and rates model [12]. For recurrent event data, the average number and the incidence of events are more intuitive and can be better explained than the risk. The model is a semi-parametric conditional survival model that can be used for data of recurrent event. Marginal hazard ratio (mHR) was used to assess the effect of each covariate on the risk of SPC. Statistical analysis was performed using R software.

3. Results

3.1. Characteristics of patients with multiple primary tumors
The study population was followed up from 1998 to 2016. Of the 389,344 female breast cancer patients, 42,020 (10.79%) patients developed subsequent primary tumors, of which the majority (38,767, 92.3%) only developed second primary cancer (Table 1). There were 3013 cases and 240 cases of third tumor and fourth tumor, respectively. Most breast cancer patients that developed subsequent primary tumors aged 50-70 years, especially in the range of 60-70 years.
Table 1. Characteristics of selected breast cancer survivors.

| Level | Overall | FBC only | 2nd tumor | 3rd tumor | 4th tumor | P value |
|-------|---------|----------|-----------|-----------|-----------|---------|
| N (%) | 389344  | 347324   | 38767     | 3013      | 240       | <0.001  |
| Age (%) |         |          |           |           |           |         |
| <50   | 110827  | 101951   | 8304      | 545       | 27        | 11.2    |
| 50~   | 110800  | 99631    | 10346     | 751       | 72        | 30.0    |
| 60~   | 98238   | 85794    | 11401     | 962       | 81        | 33.8    |
| 70~   | 69479   | 59948    | 8716      | 755       | 60        | 25.0    |
| Race (%) |         |          |           |           |           | <0.001  |
| White | 318773  | 283879   | 26604     | 2186      | 184       | 76.7    |
| Black | 39252   | 34989    | 3956      | 291       | 16        | 6.7     |
| Asian/Pacific Islander | 31319 | 28456 | 2686 | 164 | 13 | 5.4 |
| Laterality (%) |         |          |           |           |           | 0.837   |
| Left  | 197611  | 176291   | 19652     | 1540      | 128       | 53.3    |
| Right | 191733  | 171033   | 19115     | 1473      | 112       | 46.7    |
| Tumor size (%) |         |          |           |           |           | <0.001  |
| <1cm  | 75257   | 66409    | 8094      | 699       | 55        | 22.9    |
| 1~cm  | 146447  | 129717   | 15436     | 1195      | 99        | 41.2    |
| 2~cm  | 137840  | 123934   | 12843     | 984       | 79        | 32.9    |
| 5~cm  | 29800   | 27264    | 2394      | 2296      | 134       | 7.9     |
| Nodal status (%) |         |          |           |           |           | <0.001  |
| Negative | 251774 | 222800 | 26004 | 2186 | 184 | 76.7 |
| Positive | 137570 | 124524 | 12163 | 827 | 56 | 23.3 |
| HR status (%) |         |          |           |           |           | 0.715   |
| Negative | 78659  | 70149    | 7871      | 596       | 43        | 17.9    |
| Positive | 310685 | 277175 | 30896 | 2417 | 197 | 82.1 |
| Histology (%) |         |          |           |           |           | <0.001  |
| Ductal | 292135  | 261280   | 28848     | 2186      | 181       | 75.4    |
| Lobular | 30010  | 277175   | 30896     | 2417      | 197       | 82.1    |
| Mixed  | 41260   | 36467    | 4416      | 352       | 25        | 10.4    |
| Other  | 25939   | 22908    | 2786      | 229       | 16        | 6.7     |
| Grade (%) |         |          |           |           |           | <0.001  |
| I      | 76948   | 68201    | 8080      | 618       | 49        | 20.4    |
| II     | 154936  | 138002   | 15569     | 1254      | 111       | 46.2    |
| III    | 134820  | 121217   | 12600     | 938       | 65        | 27.1    |
| IV     | 4633    | 4079     | 509       | 43        | 2         | 0.8     |
| Unknown | 18007  | 15825    | 2009      | 160       | 13        | 5.4     |
| AJCC stage (%) |         |          |           |           |           | <0.001  |
| I      | 185930  | 163845   | 20281     | 1663      | 141       | 58.8    |
| II     | 144403  | 129383   | 13871     | 1064      | 85        | 35.4    |
| III    | 50601   | 46230    | 4093      | 264       | 14        | 5.8     |
| IV     | 6039    | 5723     | 304       | 12        | 0         | 0.0     |
| Unknown | 2371  | 2143     | 218       | 10        | 0         | 0.0     |
| Surgery (%) |         |          |           |           |           | <0.001  |
| No surgery | 3448  | 3239    | 197       | 12        | 0         | 0.0     |
| Lumpectomy | 224678 | 198076  | 24364    | 2064      | 174       | 72.5    |
| Mastectomy | 161218 | 146009  | 14206    | 937       | 66        | 27.5    |

Among all the subjects, white patients were the majority, and the proportion of patients with multiple primary tumors increased in the white population. There were more breast cancer patients with tumor size in range of 1~2 cm and 2~5 cm, but the prevalence of multiple primary tumors in patients with tumor size of 1-2 cm increased while decreased in patients with tumor size of 2~5 cm. 64.7% of patients showed positive in lymph node test, and the proportion of multiple primary tumors decreased in these lymph node-positive patients while increased in negative patients. In addition,
75.0% of subjects was initially diagnosed with ductal breast cancer, and 34.6% of patients with poorly differentiated tumor cells. 99.1% of the subjects underwent surgery, and the prevalence of multiple primary tumors in patients undergoing lumpectomy was increased while decreased in patients undergoing mastectomy.

3.2. Risk factors of multiple primary tumors

Advanced age, black in race, large tumor size (above 2 cm), negative HR status, mixed pathology, poor differentiated or moderately differentiated tumor cells, and lumpectomy were significantly associated with higher risk of subsequent multiple primary tumors (Table 2).

Table 2. Analysis of risk factors of multiple primary tumors: Hazard Ratios (mHR) and 95% Confidence Intervals (95% CI) from marginal means and rates model.

| Coefficient | mHR  | 95% CI                  | P       |
|-------------|------|-------------------------|---------|
| Age <50     | Ref  | 1                       |         |
| 50~         | 0.235| 1.265                   | 1.231 - 1.300 | < 0.001 |
| 60~         | 0.551| 1.735                   | 1.689 - 1.782 | < 0.001 |
| 70~         | 0.741| 2.097                   | 2.039 - 2.158 | < 0.001 |
| Race        |      |                         |         |
| White       | Ref  | 1                       |         |
| Black       | 0.160| 1.173                   |         |
| Asian/Pacific Islander | -0.110| 0.895 | 0.863 - 0.929 | < 0.001 |
| Laterality  |      |                         |         |
| Left        | Ref  | 1                       |         |
| Right       | 0    | 1                       | 0.982 - 1.019 | 0.969   |
| Tumor size  |      |                         |         |
| <1 cm       | Ref  | 1                       |         |
| 1~ cm       | -0.015| 0.985 | 0.961 - 1.011 | 0.254   |
| 2~ cm       | 0.045| 1.046                   | 1.011 - 1.083 | 0.011   |
| 5~ cm       | 0.124| 1.132                   | 1.073 - 1.195 | < 0.001 |
| Nodal status|      |                         |         |
| Positive    | Ref  | 1                       |         |
| Negative    | -0.001| 0.999 | 0.967 - 1.032 | 0.949   |
| HR status   |      |                         |         |
| Positive    | Ref  | 1                       |         |
| Negative    | 0.134| 1.144                   | 1.114 - 1.174 | < 0.001 |
| Histology   |      |                         |         |
| Ductal      | Ref  | 1                       |         |
| Lobular     | 0.019| 1.019                   | 0.982 - 1.057 | 0.313   |
| Mixed       | 0.063| 1.065                   | 1.034 - 1.097 | < 0.001 |
| Other       | 0.010| 1.010                   | 0.973 - 1.048 | 0.604   |
| Grade       |      |                         |         |
| Grade I     | Ref  | 1                       |         |
| Grade II    | 0.027| 1.028                   | 1.002 - 1.054 | 0.036   |
| Grade III   | 0.043| 1.044                   | 1.013 - 1.075 | 0.005   |
| Grade IV    | 0.069| 1.071                   | 0.985 - 1.165 | 0.109   |
| Unknown     | 0.028| 1.028                   | 0.981 - 1.078 | 0.245   |
| AJCC stage  |      |                         |         |
| Stage I     | -0.032| 0.968 | 0.933 - 1.005 | 0.086   |
| Stage II    | 0.005| 1.005                   | 0.950 - 1.063 | 0.859   |
| Stage III   | 0.094| 1.099                   | 0.976 - 1.237 | 0.120   |
| Stage IV    | -0.01| 0.990                   | 0.869 - 1.128 | 0.881   |
| Surgery     |      |                         |         |
| No          | Ref  | 1                       |         |
| Lumpectomy  | 0.149| 1.160                   | 1.014 - 1.327 | 0.031   |
| Mastectomy  | 0.014| 1.014                   | 0.886 - 1.160 | 0.837   |
Compared to patients younger than 50 years old, the risks of developing at least one new primary tumor in patients aged 50-59, 60-69, and 70 years were 1.265 times (mHR = 1.265, 95% CI: 1.231 - 1.300), 1.735 times (mHR = 1.735, 95% CI: 1.689 - 1.782) and 2.097 times (mHR = 2.097, 95% CI: 2.039 - 2.158) higher, respectively. The results were all statistically significant ($P < 0.001$, Table 2). Black women had the highest risk of multiple primary tumors (mHR = 1.173, 95% CI: 1.138 - 1.211, $P < 0.001$) compared with white women and Asian or Pacific Island women. Factors such as large breast tumor size (> 2 cm vs. <1 cm: mHR = 1.046, 95%CI: 1.011 - 1.083, $P = 0.011$; > 5 cm vs. <1 cm: mHR = 1.132, 95%CI: 1.073 - 1.195, $P < 0.001$), negative HR status (mHR = 1.144, 95%CI: 1.114 - 1.174, $P < 0.001$), mixed histology (mHR = 1.065, 1.034 - 1.097, $P < 0.001$), moderate (mHR = 1.028, 95%CI: 1.002 - 1.054, $P = 0.036$) or poor (mHR = 1.044, 95%CI: 1.013 - 1.075, $P = 0.005$) tumor differentiation, and lumpectomy (mHR = 1.160, 95%CI: 1.014 - 1.327, $P = 0.031$) were all significantly associated with increased risk of multiple primary tumors (Table 2).

4. Discussion
The marginal means and rates model used in this study is applicable to the situation where there is no time-varying covariate and the average number of events is interested to describe the risk [13]. Meanwhile, this model does not specify the covariance structure among the occurrence time of events within a subject, and therefore applies to situations where the covariance structure is complex or unknown. In addition, since the marginal means and rates model treats all recurrent events of the same individual as a single counting process and does not consider time-dependent variables to reflect the histology of the process, it is more flexible and convenient than other similar survival models for recurrent data [14].

The results of our study showed that older breast cancer patients had a higher risk of developing multiple primary tumors, which is consistent with the multivariate analysis of other studies [6, 15-17]. Aging is one of the most important risk factors for many types of cancer, which is related to factors such as adverse lifestyles, weakened immune system function, increased sensitivity to carcinogens and reduced DNA repair. Race is also an important risk factor of multiple primary tumors. The incidence and risk of subsequent primary tumors among black women is higher than that of white women and Asian or Pacific island women. Other studies have confirmed this conclusion [7, 18, 19], which may be the result of a combination of many factors such as genetic or biology factors, and socioeconomic disparities. As previous studies reported, African American with early stage primary breast cancer were more likely to receive inappropriate treatment after the initial breast cancer diagnoses [20].

Patients with negative HR breast cancer have a higher risk of developing multiple primary tumors, which still remains to be explained. Women whose first primary breast cancer was triple-negative (estrogen receptor, progesterone receptor and HER2 are all negative) had a higher risk of contralateral breast cancer compared to women with receptors-positive breast cancer. According to other studies, the increased risk of subsequent primary tumors was evident across all race/ethnicity groups for HR-negative first tumors. Besides, many treatment strategies are related to improved breast cancer outcomes, including correct classification of HR status and adherence to adjuvant hormonal therapy.

5. Conclusion
With the progress in technology of diagnosis and treatment, the survival of breast cancer patients has been significantly improved, which in turn increases the probability of developing subsequent primary tumors after initial breast cancer. The results from the survival analysis model indicated that the risk of at least developing one subsequent primary tumor in breast cancer survivors was associated with age, race, tumor size, HR status, histology type, tumor grade, and surgical type. More active clinical monitoring and follow-up should be performed on breast cancer survivors who are at higher risk of multiple primary tumors, thereby improving their prognosis and life quality.

Acknowledgments
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