Differential Second Primary Malignancy Occurrence After Breast Cancer According to HER2 Status: a SEER Population-Based Analysis

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Abstract

Background: The survival improvement in breast cancer (BC) renders the long-term survivors an increased probability of second primary malignancy (SPM), and thus excess mortality. Although previous evidence has indicated various predictors of SPM, little is known whether SPM incidence varies by HER2 status of first BC.

Methods: Based on BC patients registered between 2010-2018 in the NCI SEER database, we utilized standardized incidence ratio (SIR) and Poisson regression to quantify SPM occurrence compared with the general population. Then, adjusted for competing death risk, cumulative incidence function and Gray's test were adopted to estimate the probability of SPM. Subsequent proportional subdistribution hazards regression was executed to identify the HER2 status impact on SPM risk. Finally, survival analysis was performed.

Results: A total of 409,796 first BC patients were included and 18,283 were identified with at least one SPM. The SIR of SPM after HER2+ BC was significantly lower than HER2- BC (1.03 vs 1.13; RR, 0.92; 95% CI, 0.88-0.96; $p < 0.001$). But the predominantly declining SPM risk was only observed for second BC (RR, 0.89; 95% CI, 0.82-0.96; $p = 0.003$) and lung and bronchus cancer (RR, 0.84; 95% CI, 0.74-0.95; $p = 0.007$). Further competing risk analysis verified the protective effect of HER2 positivity status on SPM occurrence. The 5-year cumulative incidence of SPM following HER2+ and HER2- BC were 5.16% and 4.09%, respectively ($p < 0.001$). In addition, among patients suffering from SPM, HER2 positivity status contributed to better overall survival.

Conclusion: After considering intrinsic incremental risk with age and adjusting for competing risk of death, our study demonstrated that HER2+ BC patients had lower SPM occurrence, remarkable for second BC and lung and bronchus cancer. The disparity implies the relation between SPM occurrence and therapeutic along with genetic factors underlying BC HER2 status.

Background

In GLOBOCAN 2020, breast cancer (BC) has become the most frequently occurring cancer and the leading cause of cancer death in women [1]. During the past decades, dramatic survival benefit has been achieved by profound understanding of BC biology, widely applied early screening, and rapid development in the systemic therapies [2–4]. One milestone of these achievements was the recognition of overexpressed human epidermal growth factor receptor 2 (HER2) as a major driver in 18–20% of BC [5, 6]. Fortunately, anti-HER2 therapies represented by trastuzumab has become the standard treatment for HER2-positive (HER2+) BC patients and substantially improved their prognosis [7–9]. However, the favorable survival outcome renders BC patient a higher probability of second primary malignancy (SPM) occurrence [10]. A recent case-control study also reported excess risk for SPM among BC survivors [11], with an adjusted standardized incidence ratio of 12.94.

Since SPM can lead to excess mortality in BC patients[12, 13], SPM occurrence and its related risk factors raised the awareness of clinicians. For example, SPM risk decreased with age[14], with an exception of lung cancer that is aging-related[15]. Negative hormone receptor was correlated with increased risk of SPM[16–18], which probably shared the same etiologic factors with first BC. It is also reported that postoperative treatment could influence the SPM occurrence. The effect of chemotherapy remains controversial[18–20], although several literatures reached the agreement that utilization of DNA-damaging chemicals led to increased incidence of SPM[21]. Radiotherapy may subject patients to a greater risk for SPM, especially lung cancer, esophageal cancer and contralateral BC[22, 23]. Conversely, hormonal therapy exhibited a protective effect from SPM occurrence[24], though patients treated with tamoxifen had an elevated risk of corpus uteri cancer[25]. In addition, genetic alteration, particularly BRCA1/2 mutation were proven to be risk factors for SPM occurrence[24, 26]. Despite massive efforts in exploring predictors of increased SPM risk, few studies have considered the effect of HER2 status[24]. It is noteworthy that no literatures reported the association between anti-HER2 therapies and SPM incidence.

This study aimed to investigate the differential SPM occurrence after first primary BC according to HER2 status, using surveillance, epidemiology, and end results (SEER) database. We used standardized incidence ratio (SIR) to profile and compare the SPM incidence between BC patients with different HER2 status. To adjust for competing death risk, subsequent competing risk analysis was conducted to explore the role of HER2 in SPM risk. We further assessed the survival outcomes according to HER2 status and whether SPM exists or not.

Methods

Study Population

SEER*Stat software (version 8.3.9) was used to obtain the SEER 18 Registries (excluding AK) Research Data (2000–2018, based on November 2020 submission), which covers approximately 27.8% of the US population. From the cases reported to this database, we incorporated female patients older than 18 years old and diagnosed with malignant BC. The malignant cases were identified based on behavior codes in ICD-O-3. Only cases with definite HER2 and HR status diagnosed between January 1, 2010 and December 31, 2018 were selected, for SEER program did not collect HER2 status of BC before the year of 2010. Cases without positive histology and active follow-up were excluded, as well as those death certificate and autopsy only cases. Besides, patients were not included if their survival months or follow-up time was shorter than 2 months or unknown, or were diagnosed with SPM within 2 months since the date of BC diagnosis in order to exclude synchronous cancers.

Study Variables

Patients were classified into 4 groups based on the diagnosis age: <45, 45–59, 60–74, $\geq$ 75 years. Four-grade system was utilized to acquire BC grades according to microscopic examination of tumor tissue. A combined stage group was derived based on clinical and pathologic information composed of primary tumor(T), regional lymph nodes(N) and distant metastasis(M). The TNM classification followed the TNM manuals published by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), the most up-to-date edition at that time. Hormone receptor (HR) status was obtained via the immunohistochemistry test of estrogen or progesterone receptor (ER/PR)[27]. HER2 status was defined via the algorithm for deriving HER2 summary variable, according to immunohistochemistry and in situ hybridization tests[28]. The timing of the SPM and death occurrence and cause of death were also provided.

Furthermore, SEER*Stat computed the SIR to quantify the SPM incidence in first BC patients. SIR is the observed incidence of SPM among BC survivors to the expected incidence[29, 30], based on specific cancer incidence rates for the general population in SEER 18 Registries (excluding AK). The 95% CI for SIR was estimated assuming a Poisson distribution for the observed SPM numbers. SIRs of SPM following HER2-positive (HER2+) and HER2-negative (HER2-) BC patients were acquired overall and stratified by HR status, diagnosis age and malignancy site.

Statistical analysis

According to HER2 status of first BC, patient characteristics and most importantly, whether suffering from SPMs were analyzed. Pearson's chi-square test was employed to compare the variable distribution.

Due to the natural different morbidity in different cohorts, SIRs reliably manifested SPM incidence in BC survivors. With the expected numbers as an offset, Poisson regression estimated the relative risk (RR) of HER2 status, HR status and age on SPM. Since latency after first BC diagnosis varied and a large proportion of patients died before SPM occurrence, competing risk analysis was adopted to verify the risk of SPM after HER2- and HER2 + BC[31, 32]. We utilized Cumulative incidence function (CIF) to describe the occurrence, and Gray's test to assess the statistical difference of occurrence probability.

Subsequently, the hazard ratios (HRs) and 95% CIs of developing SPM after HER2 + vs. HER2- BC were calculated using proportional subdistribution hazards regression, which adjusts for competing risk of death and other significant characteristics. Regarding survival, overall survival (OS) and breast cancer-specific survival (BCSS) were calculated from the date of diagnosis of BC to the date of death, due to any causes and BC specifically. Kaplan-Meier survival analyses were utilized to estimate the OS and BCSS of BC patients based on whether SPMs exist and their intrinsic HER2 status. Log-rank tests were adopted to determine the difference significance.

All statistical analyses were performed using R version 4.0.5 software. Statistical significance was set at two-sided, with p value < 0.05 defined as statistically significant.

Results

Patient characteristics

409,796 BC patients diagnosed between 2010–2018 were selected in this study, with a median follow-up period for 44 months. HER2 + BC (N = 64,740) accounted for 15.80% of all patients, 3.54% of which (N = 2293) were reported to develop SPMs, while HER2- BC (N = 345,056) had a higher SPM incidence of 4.63% (N = 15990). Table 1 outlines the clinicopathologic characteristics and occurrence of SPM, grouped by HER2 status at first primary BC diagnosis. All factors were statistically significantly associated with HER2 status ($p < 0.001$) based on Pearson’s chi-square test. For HER2 + BC patients, 11592 (17.91%) women were diagnosed aged < 45 and 26282 (40.60%) aged between 45–59, accounting for significantly higher proportions than those with HER2- BC.

Table 1 Patients Characteristics

Characteristics	HER2 Positive	HER2 Negative	<i>p</i> -value
	64,740 (100.00)	345,056 (100.00)	
Age (years), n (%)			< 0.001
< 45	11592 (17.91)	38307 (11.10)	
45–59	26282 (40.60)	117291 (33.99)	
60–74	19906 (30.75)	133339 (38.64)	
≥ 75	6960 (10.75)	56119 (16.26)	
Grade, n (%)			< 0.001
Well differentiated	3030 (4.68)	88356 (25.61)	
Moderately differentiated	22762 (35.16)	152963 (44.33)	
Poorly differentiated/Undifferentiated	35310 (54.54)	91326 (26.47)	
Unknown	3638 (5.62)	12411 (3.60)	
Stage, n (%)			< 0.001
0/I	24020 (37.10)	181579 (52.62)	
II	23874 (36.88)	107334 (31.11)	
III	9788 (15.12)	34492 (10.00)	
IV	4997 (7.72)	13937 (4.04)	
Unknown	2061 (3.18)	7714 (2.24)	
HR status, n (%)			< 0.001
Negative	19162 (29.6)	45841 (13.29)	
Positive	45578 (70.4)	299215 (86.71)	
With SPM, n (%)			< 0.001
Yes	2293 (3.54)	15990 (4.63)	
No	62447 (96.46)	329066 (95.37)	
Abbreviations: HR hormone receptor, HER2 human epidermal growth factor receptor 2			

Besides, HER2 + BC were more likely to have advanced grade and stage, and negative HR status. However, SPMs were remarkably less common in HER2 + BC patients, despite their clinicopathologic characteristics reflect more aggressive clinical courses.

Profile of SPM incidence

18,283 patients were diagnosed with at least one SPM after 2 months of first BC diagnosis, with 19,297 SPMs overall, which was significantly more than the 17,346.64 expected cases based on the rates in the general population (SIR = 1.11; 95% CI 1.10–1.13). As listed in Table 2, compared with the general population, SPM incidence was

Table 2 Standardized incidence ratios (SIRs) of second primary malignancy (SPM) only significantly elevated following HER2- BCs, of which SIR was 1.13 (95% CI 1.11-1.14; $p < 0.05$). Based on the Poisson regression, the RR of SPMs following HER2+ versus HER2- BCs was 0.92 (95% CI 0.88-0.96; $p < 0.001$). The results were consistent in both HR status subgroups. Regarding HR status, the SPM risk for HR- versus HR+ BC patients was significantly increased, with an RR of 1.14 (95% CI 1.11-

	HER2+		HER2-		HER2+ versus HER2-		
	SIR	95% CI	SIR	95% CI	RR (95%CI)	<i>p</i> -value	RR (95%CI)
All patients	1.03	0.99-1.07	1.13*	1.11-1.14	0.92 (0.88-0.96)	<0.001	
HR status							
Positive	1.02	0.98-1.07	1.10*	1.09-1.12	0.94 (0.88-1.00)	<0.001	Reference
Negative	1.04	0.97-1.12	1.30*	1.24-1.35	0.80 (0.74-0.88)	<0.001	1.14 (1.11-1.16)
Age(years)							
<45	1.99*	1.75-2.44	2.12*	1.99-2.25	0.94 (0.82-1.07)	0.347	Reference
45-59	1.13*	1.06-1.21	1.28*	1.25-1.32	0.88 (0.82-0.95)	<0.001	0.60 (0.58-0.62)
60-74	0.87*	0.81-0.93	1.01	0.99-1.04	0.86 (0.80-0.92)	<0.001	0.47 (0.46-0.49)
≥75	0.94	0.85-1.04	1.07*	1.04-1.1	0.88 (0.79-0.98)	0.02	0.50 (0.49-0.52)

1.16; $p < 0.001$). Among BC molecular subtypes, the uppermost SIR of 1.30 (95% CI 1.24-1.35) belongs to the triple negative BC. In different age subgroups, the significantly lower SPM incidence after HER2+ BCs was only consistent in patients older than 44 years. The SPM risk also decreased as patients age. It is noteworthy that HER2+ BC patients aged 60-74 had a significantly SPM incidence reduction than the general population (SIR, 0.87; 95% CI 0.81-0.93).

The impact of HER2 status on SPM risk may differ by specific SPM types, thus SPM occurrence in different sites was then profiling. The most frequent SPM sites were female breast (N=5,499 [28.50%]), followed by lung and bronchus (N=2,388 [12.38%]),

colon (N=1129 [5.85%]), corpus uteri (N=1090 [5.65%]) and thyroid (N=968 [5.02%]). Number of patients developing SPM and the SIRs of different SPM types following HER2+ vs. HER2- BC are exhibited in Fig. 1. For HER2+ BC patients, SIRs significantly greater than 1 were only observed with second thyroid cancer, renal carcinoma, leukemia and gastric cancer (site-specific SIRs were 2.38, 1.58, 1.69 and 1.51, respectively; all $p < 0.05$). Except gastric cancer, incidence of the other three SPMs in HER2- BC survivors also significantly exceed the general population. For most SPM sites, including female breast, lung and bronchus, colon, melanoma, pancreas, SPMs with higher occurrence rates than the general population were only observed among HER2- BC patients. Poisson regression was used again to estimate different second malignancy risks according to different HER2 status. Fig. 2 demonstrated the forest plots visualizing the relative risks of HER2 positive status for SPM occurrence. Notably, only for second primary malignancies in female breast (RR, 0.89; 95% CI, 0.82-0.96;

$p=0.003$) and lung and bronchus (RR, 0.84; 95% CI, 0.74-0.95; $p=0.007$), the risks were significantly reduced after HER2+ BC in comparison to HER2- BC patients. The risk was marginally reduced for second corpus uteri cancer (RR, 0.83; 95% CI, 0.69-0.99; $p=0.041$). In addition, HER2 positive status was revealed to be a risk factor for second thyroid malignancy occurrence (RR, 1.22; 95% CI, 1.04-1.42; $p=0.015$).

Competing risk analysis

When estimating the SPM incidence, occurrence of death can compete and should be taken into account by competing risk analysis. Fig. 3 depicted the cumulative incidence of SPMs and deaths via CIF. The 5-year cumulative incidence of SPMs following first

HER2- and HER2+ BC were 5.16% and 4.09%, respectively. HER2- BC patients had a markedly higher cumulative SPM incidence than HER2+ BC patients ($p<0.001$), and on the contrary, lower significantly death incidence ($p<0.001$). To understand whether the difference of SPM cumulative incidence is solely due to the HER2 status, subdistribution hazard function was performed, as shown in Table 3. Univariate regression analysis indicated that not only HER2 status, but also age, grade, stage and HR status were correlated with SPM risk. Multivariate regression analysis further screened HER2 status and diagnosis age as independent risk factor for SPM. HER2 positive status significantly reduced the total SPM risk (sdHR, 0.86; 95% CI, 0.82-0.90; $p<0.001$), in accordance with aforementioned results. However, the inconsistency was that SPM risk increased as patients diagnosed at older age ($p<0.001$), and HR status did not differ statistically in SPM risk ($p=0.28$).

In addition, multivariate proportional subdistribution hazards regression was

Table 3 Univariate and multivariate proportional subdistribution hazard regression of second primary malignancy (SPM) in breast cancer patients.

Characteristics	Univariate	Multivariate		
	sdHR (95% CIs)	<i>p-value</i>	sdHR (95% CIs)	<i>p-value</i>
Age (years)				
<45	Reference		Reference	
45-59	1.42 (1.33, 1.51)	<0.001	1.40 (1.31, 1.49)	<0.001
60-74	2.15 (2.02, 2.28)	<0.001	2.09 (1.96, 2.22)	<0.001
≥75	2.56 (2.39, 2.74)	<0.001	2.49 (2.32, 2.67)	<0.001
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	0.93 (0.90, 0.97)	<0.001	0.98 (0.94, 1.02)	0.29
Poorly differentiated/Undifferentiated	0.81 (0.77, 0.84)	<0.001	0.94 (0.89, 0.98)	0.0043
Unknown	0.80 (0.74, 0.87)	<0.001	0.91 (0.84, 0.99)	0.024
Stage				
0/I	Reference		Reference	
II	0.91 (0.88, 0.94)	<0.001	0.98 (0.95, 1.02)	0.31
III	0.91 (0.87, 0.96)	<0.001	1.03 (0.97, 1.08)	0.36
IV	0.67 (0.61, 0.74)	<0.001	0.73 (0.66, 0.80)	<0.001
Unknown	0.83 (0.74, 0.93)	0.0016	0.85 (0.76, 0.95)	0.005
HR status				
Negative	Reference		Reference	
Positive	1.11 (1.06, 1.15)	<0.001	0.98 (0.93, 1.02)	0.28
HER2 status				
Negative	Reference		Reference	
Positive	0.77 (0.74, 0.80)	<0.001	0.86 (0.82, 0.90)	<0.001
Abbreviations:sdHR subdistribution hazard ratios,HRhormonereceptor, HER2 human epidermal growth factor receptor 2				

performed according to different SPM sites. For second primary BC, as well as lung and bronchus cancer, SPM risk decreased significantly after first HER2+ BC, with sdHR of 0.82 (95% CI, 0.75-0.89; $p<0.001$) and 0.78 (95% CI 0.68-0.90; $p<0.001$) respectively. Whereas, little variance on second corpus uteri cancer risk

were shown between different HER2 status BC patients (sdHR, 0.79; 95% CI, 0.66-0.95; $p=0.014$), and no difference on second thyroid cancer risk (sdHR, 1.18; 95% CI, 1.00-1.39; $p=0.053$).

Kaplan-Meier survival analysis

Finally, the impact of SPM and HER2 status on OS and BCSS was analyzed (Fig. 4). Among the 18,283 BC patients with SPMs, 1828 (10.00%) died of BC, whereas 3645 (19.94%) patients died of other causes. In line with previous studies, SPM was associated with prominently worse OS (HR, 2.00; 95% CI, 1.93-2.08; $p<0.0001$), but slightly worsen BCSS (HR, 1.09; 95% CI, 1.03-1.14; $p=0.0012$). The 5-year OS probability was 74.4% ($p=0.004$) and 85.5% ($p<0.001$) for BC patients with/without SPMs. We also found a substantial difference in BCSS between HER2- and HER2+ BC patients (HR, 0.79; 95% CI, 0.77-0.82; $p<0.0001$) but a minor disparity in OS (HR, 0.97; 95% CI, 0.95-1.00; $p=0.0221$). Better survival outcomes favored negative HER2 status. For BC patients followed by SPMs, reversely, positive HER2 status was associated with superior OS (5-year OS, 76.2% vs 74.2%; $p=0.0011$). However, no variance was shown regrading BCSS, indicating the survival difference may be attributed to other causes of death concerning SPM.

Discussion

In our study, we mainly focused on the association between SPM occurrence and HER2 status of first BC. Significantly increased incidence of SPM was demonstrated in HER2- BC patients. In 2015, Raffaella et al. reported that HER2 positivity was associated with increased risk of secondary digestive system and thyroid cancer[24]. Incorporating 305 cases and 1,525 control patients, this study was limited by small sample sizes. For the first time, two different methods were performed to explore the risk factors for SPM incidence. On the one hand, older age is associated with intrinsic incremental cancer risk. And HER2 status varied with age according to our baseline characteristics analysis. Therefore, SPM risk and effect of HER2 status were quantified using standardized incidence ratios (SIRs) and Poisson regression, by introducing age-specific rates in the general population as external reference. On the other hand, we further executed competing risk analysis to verify the impacts of risk factors on SPM occurrence, considering death as a competing risk. Eventually, two approaches yielded similar result that remarkable SPM risk difference existed between HER2+ and HER2- BC patients.

However, apparent discrepancy was presented for age and HR status. In the latter proportional subdistribution hazards regression, the SPM risk increased when BC patients were diagnosed at older age. But if we take the natural incremental cancer risk with age into account, totally contrary result was obtained that SPM risk declined with age. It seemed more reliable and may be attributable to the genetic predisposition of cancer in young BC patients and probable prolonged survival period. We also discovered an elevated risk of SPM among HR- BC patients as reported by previous studies[14, 17], which may due to common genetic determinants and limited treatment. Nevertheless, after adjusting for the death risk, no statistically significant result was observed between HR+ and HR- BC patients. We suspect that the non-negligible occurrence of death precluded the occurrence of SPMs, probably contributing to

an overestimation of SPM occurrence in HR- BC patients. Age could also be regarded as a confounder, since HR negative status was more common in younger BC patients[33].

Although HER2- BC was not so aggressive as HER2+ BC, the higher incidence of SPM makes it a new concern for BC survivors. As above mentioned, compared with HER2+ BC, HER2- BC patients had superior BCSS in all patients, but worse OS in patients followed by SPM. To improve the OS of HER2- BC patients, it is important to find out the potential contributing factors that are relevant to HER2 status.

In recent decades, HER2 status has been an established target in BC therapy. Biologically, HER2 exists as a driving factor in various tumor types derived from epithelia, represented by BC, non-small-cell lung cancer[34, 35], gastric and gastroesophageal junction cancers[36, 37]. It was further confirmed by the fact that HER2 overexpression or gene amplification were detected in a variety of human malignancies including lung[38], gastric[39], ovarian[40], biliary tract[41] and colorectal cancers[42]. In therapeutic application, anti-HER2 therapies have already shown efficacy in HER2-positive advanced gastric cancers[36, 43, 44]. Therefore, we speculate that when HER2+ patients undertook anti-HER2 treatment for BC, these targeting therapies would probably simultaneously extinguish and eliminate latent HER2+ transformed cells in other system. As a result, the SPM incidence decreased after HER2+ BC due to the HER2-targeted treatment. It is known that more than two decades have passed since the approval of the first anti-HER2 targeted therapy trastuzumab by FDA in 1998. And HER2-targeted treatment has become the standard care in managing HER2+ BC patients all over the world. Hence, recent calendar year and HER2 positivity diagnosis have been used as a crude proxy to support this hypothesis. Besides anti-HER2 therapy, HER2+ BC patients were more likely to receive adjuvant chemotherapy[45, 46], which may also contribute to the declining SPM incidence.

As for the intrinsic risk factors of SPM, shared genetic predisposition associated with BC HER2 status is inevitable. It has been reported that pathogenic germline variants were exhibited in 8% of adult cancer cases^[47]. Genomic alterations are also reported to be incriminated towards HER2+ BC[48, 49]. Moreover, several genes such as FCRLM1, BLK and IHGD were indicative of the development of SPMs among BC patients[48, 49]. It led to the assumption that some unique intrinsic genetic variants existed in BC patients may be a natural inclination for the SPMs. Indirect support for the hypothesis can be gleaned from the findings that higher proportion of HER2 positive status was observed in BC patients carrying BRCA2 mutations, and meanwhile, BRCA2 carriers were less likely to be diagnosed with SPMs[50]. In summary, the SPM risk reduction after HER2+ BC may be attributable to the widespread anti-HER2 treatment combined with chemotherapy, as well as genetic susceptibility. More investigation about therapeutic and inherent factors should be conducted to reveal the disparity between different BC HER2 status.

The differential SPM occurrence following HER2+ and HER2- BC was comprehensively profiled in this context. It was based on a large population cohort from SEER program, thus minimizing the sampling error and ensuring the quality of the data. However, there were still some limitations. First, some metastasis and relapse may be mistaken as SPM. Although we excluded the cases within 2 months since BC diagnosis to avoid synchronous cancers. Second, because of data incompleteness, we could not

analyze effects of adjuvant treatment, especially anti-HER2 therapies. Third, data on some potential risk factors was not available, such as smoking, alcohol use and body mass index. More researches with detailed information on treatment delivery, genetic variants and other confounders are needed to reveal the disparity.

In conclusion, SPM incidence significantly declined after HER2+ BC, demonstrated by different quantitative tools including SIR and competing risk model. The OS deterioration in HER2- BC patients accompanied by SPM indicated the requirement to explain this disparity, with the aim of reducing SPM risk. We suggested that the differential SPM occurrence could be attributable to HER2-targeted therapy combined with chemotherapy, and inherent genetic factors, both of which are closely related to HER2 status of first BC. Further studies are required to prove this plausible hypothesis.

Declarations

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Authors' contributions

GZ, NL and XYL designed the study. XYL, XL and GW contributed to the data acquisition, statistical analysis and interpretation. XYL and JL drafted the manuscript. GZ and NL revised the article. All authors contributed to the article and approved the submitted version.

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Availability of data and materials

The dataset supporting the conclusions of this article is available in the SEER*Stat software (version 8.3.9) after providing submit request at <https://seer.cancer.gov/seertrack/data/request/>.

Ethics approval and consent to participate

Since SEER database is publicly available, this study was exempt from ethical approval or patients' consent.

Consent for publication

Informed consent for publication was obtained from all authors.

Competing interests

The authors declared that they have no competing interests.

Abbreviations

HRhormonereceptor, HER2 human epidermal growth factor receptor 2, SIR standardized incidence ratio, CI, confidence interval, RR relative risk, *p value<0.05

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Figures

Figure 1

Standardized incidence ratios (SIRs) and patient numbers of second primary malignancies (SPM) in specific sites.

Figure 2

Site-specific Standardized incidence ratios (SIRs) and relative risks of developing second primary malignancies (SPM) after HER2+/HER2- BCs.

Figure 3

Cumulative incidence curves for second primary malignancies and deaths in HER2+ and HER2- breast cancer patients.

Figure 4

Survival curves of OS and BCSS based on (a, b) SPM occurrence; (c, d) HER2 status in all patients and (e, f) HER2 status in patients with SPMs.