Original Article

Characteristics and survival analysis of breast cancer survivors with metachronous double primary cancers: a retrospective cohort study

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Background: Breast cancer (BC) is the most frequently diagnosed malignancies in females, and its incidence has increased dramatically recently. Clinical studies have shown that BC patients are developing double primary cancers more frequently than by chance, and the prognosis has changed greatly. Previous articles rarely mentioned metachronous double primary cancers in BC survivors. Thus, further analysis of the clinical characteristics and survival differences may provide valuable information in BC survivors.

Methods: In this study, we retrospectively analyzed 639 cases of double primary cancers in BC patients. Cox univariate and multivariate regression analyses of clinical factors of overall survival (OS) were performed in patients with double primary cancers when breast cancer was the primary tumor to assess the correlation between clinical factors and OS in these patients with double primary cancers.

Results: Among the double primary cancer patients, BC was the most frequent first primary cancer. In terms of numbers, thyroid cancer was the most common type of double primary cancer among BC survivors. Patients had a younger median age when BC occurred as the first primary cancer rather than the second primary cancer. The total mean time interval between the onset of double primary tumors was 70.8 months. With the exception of the thyroid and cervical cancer, the incidence of second primary tumors was <60% within 5 years. However, the incidence was >60% within 10 years. The mean OS of double primary cancer patients was 109.8 months. Additionally, patients who had thyroid cancer as their second primary cancer had the highest 5-year survival rate, followed by cervical, colon, and endometrial cancer, while patients who had lung cancer as their second primary cancer had the lowest 5-year survival rate. OS risk of BC survivors with second primary cancers was significantly associated with age, menopause status, family history, tumor size, lymph node metastasis, and human epidermal growth factor receptor 2 (HER2) status.

Conclusions: The identification of double primary cancers in earlier stages could play a critical role in guidance and lead to better outcomes. A prolonged follow-up examination period for BC survivors is needed to provide better guidance and treatments.

Keywords: Breast cancer (BC); double primary cancers; clinical characteristics; overall survival (OS)

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Introduction

Breast cancer (BC) is one of the most frequently diagnosed malignancies in females worldwide, and its incidence has continued to increase dramatically in recent decades (1,2). According to an epidemiological study, there were almost 2.1 million newly diagnosed cases in 2018 (3). The survival of BC patients has improved significantly due to breakthroughs in early detection and comprehensive adjuvant therapies (4). However, with improved survival, the incidence of double primary cancers in BC survivors has also increased significantly (5-7). Clinical studies have shown that BC patients are developing double primary cancers more frequently than by chance (8,9), and consequently, the prognosis of such patients has changed greatly.

We find that although previous articles have mentioned the relationship between BC and metachronous double primary cancers (MDPCs), such as studies finding that patients with breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) mutations are predisposed to BC associated with ovarian cancer, patients with both BC and thyroid cancer typically have worse survival than those with only BC or thyroid cancer, whereas in the MDPCs of both BC and colorectal cancer, human epidermal growth factor receptor 2 (HER2) positivity and colorectal cancer lymph node metastasis may be prognostic factors that affect overall survival in these patients. However, studies on survival and prognosis of MDPCs have not been found. In clinical practice, the occurrence of metachronous double primary cancers is common. However, most of the reports about metachronous double primary cancers are case reports. Other studies covered fewer types of cancers (10). Investigating the risk factors and prognosis associated with metachronous primary cancer can increase awareness the identification of double primary cancers in earlier stages could play a critical role in guidance and lead to better health outcomes. Patients with dual primary cancers are sometimes misdiagnosed as having recurrence or metastasis. The treatment of primary cancers is completely different from that of recurrent and metastatic cancers, and the optimal period for radical treatment can be easily missed. The aim of our study was to further analyse the clinical characteristics and survival differences in The Third Affiliated Hospital of Harbin Medical University. Thus, the early detection and diagnosis of double primary cancers can improve the prognosis (11,12) and quality of life of patients. Patients with metachronous cancer are defined as those diagnosed with a secondary cancer 6 months or more after their primary cancer diagnosis. Increased awareness and the identification of double primary cancers in earlier stages could play a critical role in guidance and lead to better health outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-301/rc).

Highlight box

Key findings

- Breast cancer (BC) was always the first primary neoplasm in metachronous double primary cancer (MDPC) survivors. The most frequent double primary tumor sites in BC patients were the thyroid, ovary, cervix, lung, and endometrium. The overall survival of different types of double primary cancer patients differed significantly.

What is known and what is new?

- Advances in early diagnosis and comprehensive adjuvant therapies have significantly prolonged the OS of BC patients. However, a clinical dilemma always arises when these survivors acquire double primary tumors.
- BC survivors with thyroid cancer had the highest incidence among numerous types of double primary cancers.

What is known and what is new?

- Increased awareness and the identification of double primary cancers in earlier stages could play a critical role in guidance and lead to better health outcomes.

Methods

Study patients

This retrospective study was conducted at The Third Affiliated Hospital of Harbin Medical University. The data of 639 female double primary cancer patients, who had been treated at the hospital database between 1986 and 2011, were retrieved. The 639 patients included BC patients, and patients were included regardless of whether or not BC was the first primary tumor. The flow chart in *Figure 1* shows the screening process. This study followed the tenets of

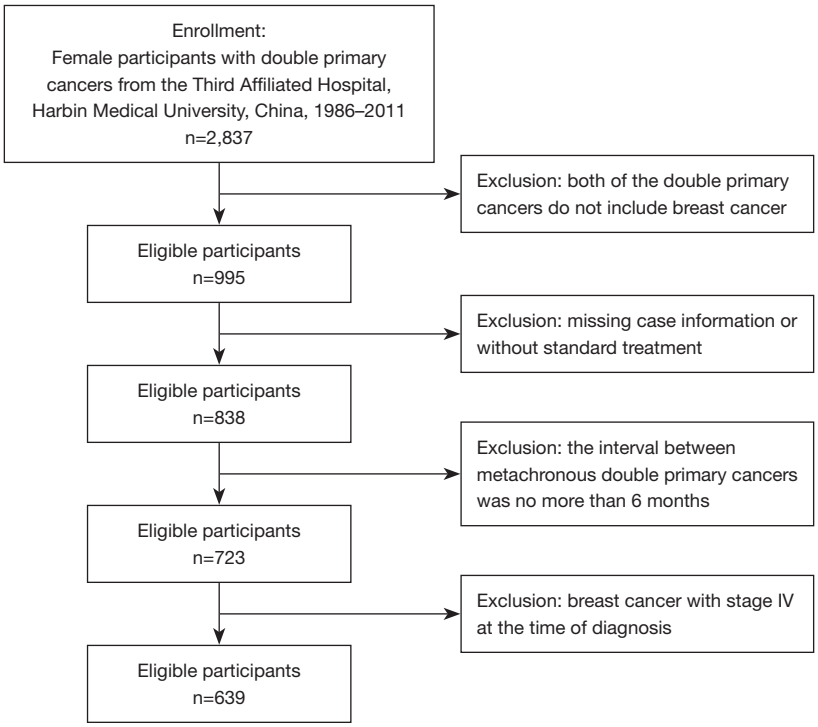

Figure 1 The process used to screen patients of breast cancer with metachronous double primary cancers.

the Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of The Third Affiliated Hospital of Harbin Medical University (No. KY2018-06). The patients provided their written informed consent to participate in the study.

Data collection

The clinicopathological characteristics, such as height (meters), weight (kilograms), age at diagnosis, menopause status, smoking history, family history, tumor size, lymph node metastasis, estrogen receptor, progesterone receptor, and HER2 status, of the BC survivors were collected. Body mass index (BMI) was calculated as weight divided by height (in meters squared). A BMI <25 kg/m^2 was categorized as under-/normal weight, and a BMI ≥25 kg/m^2 was categorized as overweight/obese. As per the guidelines of the World Health Organization (WHO), menopause was defined as 12 consecutive months of amenorrhea except for other pathological or physiological reasons, such as the surgical removal of the bilateral ovaries (or the uterus), or the iatrogenic cessation of ovarian function (due to medication, chemotherapy, or radiotherapy, etc.).

Patients who had been diagnosed with double primary malignancies were included in the study if they met the following inclusion criteria: (I) the malignancy of each kind of tumor had a distinct histological confirmation; (II) the patient had received standardized treatment; and (III) the interval between MDPCs was ≥6 months, which ruled out the probability of one primary cancer being the metastasis or recurrence of the other primary cancer. For example, the time interval rules and survival outcomes of individuals with metachronous breast cancer and ovarian cancer was ≥6 months as other cancers. Patients with stage IV BC at the time of diagnosis were excluded from the study.

Patients eligible for inclusion were followed up and recorded by telephone interview per six months. Follow-up information included patients' tumor recurrence and metastasis, survival status and other items. The time of last follow up was December 31, 2015.

Statistical analysis

SPSS 22.0 software was used for the statistical analyses. The continuous variables were compared using the independent 2-sample *t*-test. The endpoint was the overall survival (OS), which was calculated from the date of surgical treatment to the date of death. Survival curves were plotted using

Table 1 The distribution of the number of double primary cancers in breast cancer patients

Cancer types	All, n (%)	1st primary breast cancer, n (%)	2nd primary breast cancer, n (%)
Thyroid cancer	157 (24.57)	131 (24.86)	26 (23.21)
Contralateral breast cancer	28 (4.38)	28 (5.31)	0 (0.00)
Lung cancer	84 (13.15)	74 (14.04)	10 (8.93)
The female reproductive system			
Cervical cancer	88 (13.77)	61 (11.57)	27 (24.11)
Endometrial cancer	43 (6.73)	37 (7.02)	6 (5.36)
Ovarian cancer	119 (18.62)	98 (18.60)	21 (18.75)
The digestive system			
Esophageal cancer	3 (0.47)	3 (0.57)	0 (0.00)
Colon cancer	24 (3.76)	16 (3.04)	8 (7.14)
Rectal cancer	31 (4.85)	26 (4.93)	5 (4.46)
Stomach cancer	19 (2.97)	18 (3.42)	1 (0.89)
Pancreatic cancer	3 (0.47)	3 (0.57)	0 (0.00)
Hepatocellular cancer	4 (0.63)	3 (0.57)	1 (0.89)
The urinary system			
Renal cell cancer	9 (1.41)	5 (0.95)	4 (3.57)
Ureteral cancer	1 (0.16)	1 (0.19)	0 (0.00)
Bladder cancer	5 (0.78)	4 (0.76)	1 (0.89)
Lymphoma	8 (1.25)	8 (1.52)	0 (0.00)
Laryngeal cancer	1 (0.16)	1 (0.19)	0 (0.00)
Nasopharyngeal cancer	1 (0.16)	0 (0.00)	1 (0.89)
Oropharyngeal cancer	1 (0.16)	1 (0.19)	0 (0.00)
Tonsil cancer	1 (0.16)	1 (0.19)	0 (0.00)
Soft tissue sarcoma	7 (1.10)	6 (1.14)	1 (0.89)
Melanoma	2 (0.31)	2 (0.38)	0 (0.00)
Total	639 (100.00)	527 (82.47)	112 (17.53)

the Kaplan-Meier method, and group differences in the survival curves were investigated by the log-rank test. Cox regression analysis was used for univariate and multivariate analyses. A Cox proportional-hazard model was used to identify variables that were independently associated with OS. All the statistical tests were 2-sided, and a P value <0.05 was considered statistically significant.

The missing data belong to a small sample, so we choose the simple deletion method to deal with the missing data. This method is the most primitive and efficient way to deal with missing values.

Results

The number distribution characteristics of BC patients accompanied with the other primary cancers

The number and proportion of patients with BC accompanied with other primary cancers are summarized in *Table 1*. Among the double primary cancer patients, BC was the most frequent first primary cancer (82.47%). In terms of numbers, thyroid cancer was the most common type of double primary cancers among the BC survivors, accounting for 24.57% of cases, followed by ovarian (18.62%), cervical

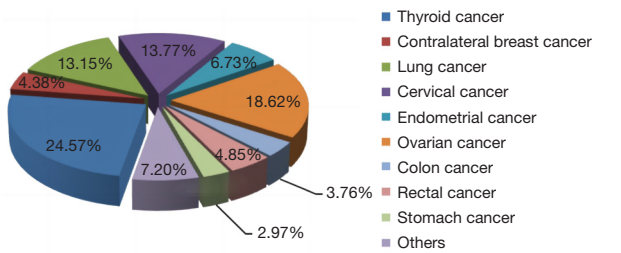

Figure 2 The percentages of double primary cancers in breast cancer patients.

Table 2 The time interval between the first primary breast cancer and the second primary cancer

Cancer type	The mean interval time (months)
Thyroid cancer	35.8
Contralateral breast cancer	79.6
Lung cancer	85.4
The female reproductive system	
Cervical cancer	62.6
Endometrial cancer	67.8
Ovarian cancer	92.4
The digestive system	
Esophageal cancer	117.0
Colon cancer	100.6
Rectal cancer	92.2
Stomach cancer	84.8
Pancreatic cancer	143.7
Hepatocellular cancer	88.3
The urinary system	
Renal cell cancer	44.8
Ureteral cancer	75.0
Bladder cancer	49.5
Lymphoma	106.5
Laryngeal cancer	41.0
Nasopharyngeal cancer	–
Oropharyngeal cancer	140.0
Tonsil cancer	36.0
Soft tissue sarcoma	56.5
Melanoma	107.0
Total	70.8

Table 3 The incidence rates of the second primary tumor within 5 or 10 years of the diagnosis of breast cancer

Common cancer types	The incidence within 5 years (%)	The incidence within 10 years (%)
Thyroid cancer	80.9	96.2
Contralateral breast cancer	57.1	71.4
Lung cancer	37.8	74.3
Cervical cancer	60.7	78.7
Endometrial cancer	59.5	83.8
Ovarian cancer	52.0	67.3
Colon cancer	50.0	68.8
Rectal cancer	34.6	76.9
Stomach cancer	44.4	77.8

(13.77%), lung (13.15%), and endometrial (6.73%) cancer. Conversely, digestive system cancers, such as colon (3.76%) and rectal (4.85%) cancers, were rare (*Table 1*). For more details, see *Figure 2*.

The time interval between the onset of double primary tumors and the incidence of the second primary tumor within 5 or 10 years when BC was the first primary tumor

For the second primary cancer, the time interval relative to the occurrence of the first primary BC varied depending on the type of tumor. As *Table 2* shows, the total mean time interval was 70.8 months (range, 7 to 397 months). Conversely, thyroid cancer (35.8 months) was diagnosed significantly earlier than other tumors, followed by tonsil cancer (36.0 months), laryngeal cancer (41.0 months), and renal cell cancer (44.8 months), while pancreatic cancer (143.7 months), oropharyngeal cancer (140 months), and esophageal cancer (117 months) were diagnosed later.

For BC survivors, the incidence rates for the second primary tumor within 5 or 10 years are shown in *Table 3*. With the exception of thyroid (80.9%) and cervical (60.7%) cancers, the incidence of second primary tumors was <60% within 5 years. However, the incidence was >60% within 10 years. These results suggest that clinicians and BC survivors should adopt a prolonged follow-up time to enable the earlier detection of other primary tumors.

Cox univariate and multivariate regression analyses of the clinical factors for OS in double primary cancer patients when BC was the first primary tumor

Cox univariate and multivariate regression analyses were conducted to evaluate the strength of correlations between the clinical factors of these breast cancer survivors with a second primary cancer and OS (*Table 4*). The univariate regression analysis results showed that the OS risk of BC survivors with second primary cancers was significantly associated with age [hazard ratio (HR) =0.413, P<0.001], menopause status (HR =0.453, P<0.001), family history (HR =1.717, P=0.002), tumor size (HR =1.477, P=0.021), lymph node metastasis (HR =1.421, P=0.038), and HER2 status (HR =1.996, P<0.001). No prominent correlations were observed between BMI (HR =0.953, P=0.767), smoking history (HR =0.722, P=0.180), estrogen receptor status (HR =1.307, P=0.132), or progesterone receptor status (HR =0.858, P=0.340), and OS in these double primary cancer patients. In the multivariate regression analysis, which included these variables, age (HR =0.525, P=0.003), family history (HR =1.426, P=0.041), and HER2 status (HR =1.713, P=0.017) remained significant factors affecting the OS of BC survivors with second primary cancers.

Kaplan-Meier OS curves and the 5-year survival rates of double primary cancer patients when BC was the first primary cancer

The mean OS time of double primary cancer patients was 109.8 (76.79%) months (the data are not shown). The OS curves of the first primary BC survivors with the other primary cancers are shown in *Figure 3A*, and cancer-specific survival curves are shown in *Figure 3B*. There were significant differences among the different types of double primary cancers (log-rank P<0.001). The 5-year survival rates of BC survivors with second primary cancers are summarized in *Table 5*. Patients who had thyroid cancer as their second primary cancer had the highest 5-year survival rate (89.6%), followed by cervical (75.3%), colon (73.9%), and endometrial (72.2%) cancers, while patients who had lung cancer as their second primary cancer had the lowest 5-year survival rate (21.5%). These results suggest that survival mainly depends on the type of the second primary tumor.

Discussion

BC is one of the most common malignancies diagnosed in women (13) and is also a major public health problem worldwide (3). In recent years, advances in early diagnosis and comprehensive adjuvant therapies have significantly prolonged the OS of BC patients (14). However, a clinical dilemma always arises when these survivors acquire double primary tumors (15,16). To date, most relevant studies have been controversial case reports, but research on double primary tumors has been increasing (17).

In this study, we collected and analyzed 639 cases of MDPC patients, including BC patients and patients who had BC or another cancer as their first primary tumor. The result showed that BC was often the first primary tumor, which is consistent with the results reported in other articles (18). We discovered that BC survivors had the greatest risk for developing thyroid, ovarian, cervical, lung, endometrial, and contralateral BC. Our conclusion is comparable to other reports on the second primary cancer type. However, while our results overlap with other studies, the findings are not completely consistent (18-21), and there are, of course, reports to the contrary (22). One study reported that thyroid cancer did not affect the prognosis of patients with breast cancer. The inconsistent results may be due to the small number of samples and inconsistent inclusion criteria involving patients with stage IV disease.

The etiology and pathogenesis of double primary tumors are still unclear. They are generally regarded as a combination of multiple factors. One of the most likely causes of double primary tumors is the internal factors of the organism, such as genetic mutations. Mutations of the same gene can result in cancers happened in different places. As far as our results are concerned, BRCA1 and BRCA2 are thought to be BC genes, and these 2 genes are also associated with ovarian (23,24) and lung (25) cancers. Other studies have reported that the risk of both breast and thyroid cancers increase because of the genetic mutation phosphatase and tensin homolog deleted on chromosome ten (PTEN) (8,26). Thus, changes in genetic background may lead to a high incidence of ovarian, lung, and thyroid cancers in BC survivors. Endocrine disorders also have hidden dangers for double primary tumors. In our study, with the exception of lung cancer, the most common second primary cancers were almost all hormone-related tumors. Thus, BC appears to change the balance of a woman's endocrine system. In other words, endocrine disorders may not only lead to BC but may also lead to the development of other endocrine tumors.

Comprehensive adjuvant therapies, especially chemotherapy and radiotherapy, are other "killers" that

Table 4 The Cox univariate and multivariate regression analyses of the clinical factors for OS in breast cancer survivors with a second primary cancer

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
BMI, kg/m^2		0.767		
<25	1			
≥25	0.953 (0.693–1.310)			
Age, years		<0.001		0.003
≤50	1		1	
>50	0.413 (0.302–0.565)		0.525 (0.342–0.807)	
Menopause status		<0.001		0.070
Premenopausal	1		1	
Postmenopausal	0.453 (0.334–0.614)		0.681 (0.449–1.032)	
Smoking history		0.180		
No	1			
Yes	0.722 (0.448–1.163)			
Family history		0.002		0.041
No	1		1	
Yes	1.717 (1.229–2.399)		1.426 (1.015–2.005)	
Tumor size (cm)		0.021		0.440
≤2	1		1	
>2	1.477 (1.061–2.056)		1.166 (0.789–1.723)	
Lymph node metastasis		0.038		0.061
No	1		1	
Yes	1.421 (1.020–1.979)		1.382 (0.986–1.936)	
ER		0.132		
No	1			
Yes	1.307 (0.923–1.850)			
PR		0.340		
No	1			
Yes	0.858 (0.627–1.175)			
HER2		<0.001		0.017
No	1		1	
Yes	1.996 (1.377–2.894)		1.713 (1.100–2.665)	

OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

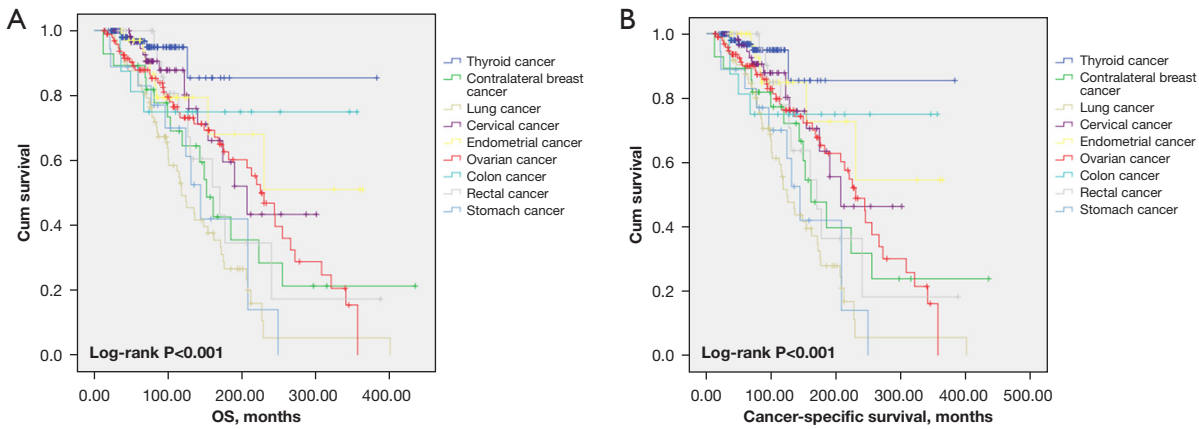

Figure 3 Kaplan-Meier survival curve for OS and cancer-specific survival in the first primary breast cancer patients with other primary cancers. (A) Kaplan-Meier survival curve for OS; (B) Kaplan-Meier survival curve for cancer-specific survival. OS, overall survival.

Table 5 The 5-year survival rates of the first primary breast cancer survivors with another primary cancer.

Common cancer type	5-year survival rate (%)
Thyroid cancer	89.6
Contralateral breast cancer	59.7
Lung cancer	21.5
Cervical cancer	75.3
Endometrial cancer	72.2
Ovarian cancer	48.0
Colon cancer	73.9
Rectal cancer	45.9
Stomach cancer	42.1

threaten patients' health. Many studies have reported that chemotherapy and radiotherapy increased the risk of the second primary tumor. Deoxyribonucleic acid damage as a consequence of chemotherapy (27) or radiation (28) may lead to a loss of genetic material, resulting in chromosomal aberrations. Research continues to be conducted to determine the lowest effective dose of radiation to provide lasting treatment to minimize the carcinogenic effects of radiation (29). Other factors, such as environmental factors and harmful lifestyle choices (30,31), have also been reported as causes of double primary cancers.

In our study, we found that BC survivors with thyroid cancer had a number of notable characteristics. We find that the survival of breast cancer patients with thyroid cancer is better than that of breast cancer patients, so we need to further study the mechanism of the conclusion to help us plan and carry out adequate and timely surveillance programs and preventive measures in clinical practice. BC patients had the youngest age of onset, and the time interval between the onset of double primary cancers was the shortest. Further, these patients had the highest 5-year survival rate, even compared to that of simple BC. Lei *et al.* reported better survival in BC survivors with thyroid cancer in 2019 (21). It is not yet known why thyroid cancer is so "active" in BC survivors. Several studies have reported on the relationship between BC and thyroid cancer and analyzed patients' clinical characteristics and survival differences (32-34), but the specific mechanism has yet to be explored. Thus, in the future, we intend to explore the mechanism underlying the internal connection between these 2 malignancies.

The results of the univariate and multivariate regression analyses showed that age, family history, and HER2 status were independent risk factors for the OS of double primary cancer patients. The Kaplan-Meier OS curve revealed significant differences in the OS of different types of double primary cancer patients. Patient prognosis was also affected by the anatomic sites of the double primary tumors. These independent risk factors can help stratify the patients into high or low-risk groups. If we pay more attention to patients with these independent risk factors, we could give patients earlier clinical intervention to prolong their survival.

This study had several limitations. First, the sample size was not sufficiently large. Second, this study was a single-center study. Thus, the epidemiological findings need to be

repeatedly verified in a wider population sample. Finally, all of the participants were Chinese, which may limit the generalizability of the results to other races.

Conclusions

To avoid delays in the treatment of second primary tumors, double primary cancers need to be identified in the clinic and should not simply be regarded as metastatic cancers. A prolonged follow-up examination period for BC survivors needs to be adopted to provide better guidance and treatments.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-301/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-301/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-301/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study followed the tenets of the Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of The Third Affiliated Hospital of Harbin Medical University (No. KY2018-06). The patients provided their written informed consent to participate in the study.

References

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69:438-51.
2. Lan NH, Laohasiriwong W, Stewart JF. Survival probability and prognostic factors for breast cancer patients in Vietnam. Glob Health Action 2013;6:1-9.
3. Chen Z, Xu L, Shi W, et al. Trends of female and male breast cancer incidence at the global, regional, and national levels, 1990-2017. Breast Cancer Res Treat 2020;180:481-90.
4. Houghton SC, Hankinson SE. Cancer Progress and Priorities: Breast Cancer. Cancer Epidemiol Biomarkers Prev 2021;30:822-44.
5. Jung HK, Park S, Kim NW, et al. Development of second primary cancer in Korean breast cancer survivors. Ann Surg Treat Res 2017;93:287-92.
6. Marcu LG, Santos A, Bezak E. Risk of second primary cancer after breast cancer treatment. Eur J Cancer Care (Engl) 2014;23:51-64.
7. Li S, Xie F, Li Y, et al. Contralateral axillary lymph node metastasis and molecular changes in second primary breast cancer: a case report. Gland Surg 2021;10:1547-52
8. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. Br J Cancer 2006;94:1745-50.
9. Bagri PK, Singh D, Singhal MK, et al. Double primary malignancies: a clinical & pathological analysis report from a regional cancer institute in India. Iran J Cancer Prev 2014;7:66-72.
10. Lee H, Lee HW, Park EJ, et al. Clinicopathologic characteristics and survival of patients with double primary malignancies: breast and colorectal cancer. Ann Coloproctol 2022;38:197-206.
11. Anderson BO, Yip CH, Smith RA, et al. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer 2008;113:2221-43.
12. Xing Y, Meng Q, Sun L, et al. Survival analysis of patients with unilateral and bilateral primary breast cancer in

Northeast China. Breast Cancer 2015;22:536-43.
13. Gao J, Liu J, Xie F, et al. Co-Delivery of Docetaxel and Salinomycin to Target Both Breast Cancer Cells and Stem Cells by PLGA/TPGS Nanoparticles. Int J Nanomedicine 2019;14:9199-216.
14. Dong C, Chen Y, Ma J, et al. Econazole nitrate reversed the resistance of breast cancer cells to Adriamycin through inhibiting the PI3K/AKT signaling pathway. Am J Cancer Res 2020;10:263-74.
15. Grundmann RT, Meyer F. Second primary malignancy among cancer survivors - epidemiology, prognosis and clinical relevance. Zentralbl Chir 2012;137:565-74.
16. Molina-Montes E, Pollán M, Payer T, et al. Risk of second primary cancer among women with breast cancer: a population-based study in Granada (Spain). Gynecol Oncol 2013;130:340-5.
17. Nishiyama K, Kamei Y, Kusakabe E, et al. A Treatment Strategy against Double Presentation of Breast Cancer and Malignant Lymphoma. Gan To Kagaku Ryoho 2018;45:1347-51.
18. Kim BK, Oh SJ, Song JY, et al. Clinical Characteristics and Prognosis Associated with Multiple Primary Cancers in Breast Cancer Patients. J Breast Cancer 2018;21:62-9.
19. Kim JY, Song HS. Metachronous double primary cancer after treatment of breast cancer. Cancer Res Treat 2015;47:64-71.
20. Schenker JG, Levinsky R, Ohel G. Multiple primary malignant neoplasms in breast cancer patients in Israel. Cancer 1984;54:145-50.
21. Lei K, He X, Yu L, et al. Breast cancer prognosis is better in patients who develop subsequent metachronous thyroid cancer. PLoS One 2019;14:e0215948.
22. Moran T, Quiroga V, Cirauqui B, et al. A Single-Center Retrospective Study of Patients with Double Primary Cancers: Breast Cancer and EGFR-Mutant Non-Small Cell Lung Cancer. Oncol Res Treat 2019;42:107-14.
23. Choi YH, Terry MB, Daly MB, et al. Association of Risk-Reducing Salpingo-Oophorectomy With Breast Cancer Risk in Women With BRCA1 and BRCA2 Pathogenic Variants. JAMA Oncol 2021;7:585-92.
24. Cvelbar M, Ursic-Vrscaj M, Rakar S. Risk factors and prognostic factors in patients with double primary cancer: epithelial ovarian cancer and breast cancer. Eur J Gynaecol Oncol 2005;26:59-63.
25. Sanchis-Borja M, Fallet V, Fabre E, et al. Characterization of lung cancers in patients with BRCA germline variants: A multicenter series. Lung Cancer 2022;173:67-70.
26. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18:400-7.
27. Travis LB, Rabkin CS, Brown LM, et al. Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. J Natl Cancer Inst 2006;98:15-25.
28. Bhatia S. Genetic variation as a modifier of association between therapeutic exposure and subsequent malignant neoplasms in cancer survivors. Cancer 2015;121:648-63.
29. Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 2011;12:353-60.
30. Begg CB, Zhang ZF, Sun M, et al. Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the Surveillance, Epidemiology, and End Results (SEER) program. Am J Epidemiol 1995;142:653-65.
31. Aredo JV, Luo SJ, Gardner RM, et al. Tobacco Smoking and Risk of Second Primary Lung Cancer. J Thorac Oncol 2021;16:968-79.
32. Zhang L, Wu Y, Liu F, et al. Characteristics and survival of patients with metachronous or synchronous double primary malignancies: breast and thyroid cancer. Oncotarget 2016;7:52450-9.
33. An JH, Hwangbo Y, Ahn HY, et al. A Possible Association Between Thyroid Cancer and Breast Cancer. Thyroid 2015;25:1330-8.
34. Kuo JH, Chabot JA, Lee JA. Breast cancer in thyroid cancer survivors: An analysis of the Surveillance, Epidemiology, and End Results-9 database. Surgery 2016;159:23-9.

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