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Original Article

Characteristics and clinical prognosis of breast cancer patients diagnosed with second primary thyroid cancer: a pilot study

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Abstract: A large number of studies have reported an association between breast cancer and thyroid cancer. The aim of this study is to assess the clinicopathological features and prognosis of breast cancer patients who developed second primary thyroid cancer. Our study analyzes and compares the following groups: (i) 52 female patients diagnosed with breast cancer and thyroid cancer simultaneously or successively (named BCTC group) from January 2011 to December 2014, (ii) among these, 26 breast cancer patients with second primary thyroid cancer subsequently (named BTC group) and (iii) 144 patients who were diagnosed with breast cancer alone (named BC group) during the same period as control. In comparison with BC group, later first pregnancy age (mean age: 26.2 v.s. 24.5, P=0.012), smaller breast tumor (T≤2 centimeters 73.1% v.s. 43.1%, P=0.005) and earlier stage (TNM stage III 7.7% v.s. 21.5%, P=0.01) were identified in BTC group. In Kaplan-Meier curve, a higher 3-year disease free survival (DFS) rate in BCTC group (94.1% v.s. 84.7%) was observed, but the log-rank test did not show significant difference in 3-year disease-free survival (DFS) between BCTC group and BC group (P=0.145). Our results indicate that reproductive factors may play a role in the etiology of thyroid cancer in breast cancer patients and suggest the female with a history of early stage breast cancer may be predisposed to develop thyroid cancer. From our pilot study, we suggest thyroid ultrasound may be applied to the routine follow-up after surgical intervention for breast cancer, but further more studies are required to prove it.

Keywords: Breast, carcinoma, human epidermal growth factor receptor 2, thyroid

Introduction

The morbidity of breast cancer has been increasing year by year and has become the most threat to women. Fortunately, the mortality of breast cancer has decreased attributing to the various therapeutic methods [1]. However, the incidence of a second primary malignancy has increased accompanying by the increasing overall survival of breast cancer.

Thyroid cancer is not rare as a second primary malignancy in the female in previous epidemiological studies [2-4]. Since 19th century many researchers have paid attention to the relationship between thyroid and mammary gland. Lots of papers have indicated that thyroid dysfunction is closely associated with breast cancer [5, 6]. The latest literature, a meta-analysis, including a total of 18 studies, has claimed the close association between the two primary cancers again [7]. However, how these two cancers may affect each other has been still poorly understood. For example, whether the treatments of breast cancer influence the development of thyroid cancer is still in debate, and the characteristics of breast cancer subsequently developing thyroid cancer is also confusing. Some experts have speculated that women with human epidermal growth factor receptor (HER)-2 positive breast cancer may be predisposed to develop malignant disease of thyroid [8-10]. But this speculation has just been derived from several case reports without population-based study. To our knowledge, none have systematically

Table 1. Patient characteristics (n=196)

Characteristic	n (%)
Age of breast cancer diagnosis (years)	Mean age 51.5 (range age 28-78)
History of smoke	
Yes	10 (5.1%)
No	186 (94.9%)
Family history of tumor	
Yes	52 (26.5%)
No	144 (73.5%)
Menopause status at breast cancer diagnosis	
Yes	90 (45.9%)
No	106 (54.1%)
Tumor size	
≤2 cm	98 (50%)
>2 cm	98 (50%)
Histological grade	
I-II	160 (81.6%)
III	36 (18.4%)
Axillary lymph nodes status	
N0	104 (53.1%)
N1-3	92 (46.9%)
TNM stage of breast cancer	
Stage I	58 (29.6%)
Stage II	102 (52.0%)
Stage III	32 (18.4%)
Pathology of breast cancer	
Invasive ductal carcinoma	171 (87.2%)
Others	25 (12.8%)
Estrogen status	
(+)	157 (80.1%)
(-)	39 (19.9%)
Her-2 status	
(+)	32 (16.3%)
(-)	163 (83.7%)
Molecular subtypes	
Luminal A	41 (20.9%)
Luminal B	109 (55.6%)
Her-2 overexpression	15 (7.6%)
TNBC	24 (15.9%)
Operation methods	
Modified radical mastectomy	180 (91.8%)
Breast conserving surgery	16 (8.2%)
Radiotherapy	
Yes	52 (26.5%)
No	144 (73.5%)

studied the demographics and clinicopathological features of breast cancer patients who were diagnosed with thyroid cancer in the follow-up time. This study compares breast cancer patients diagnosed with second primary thyroid cancer with the control group, and aims to find out the potential relationship between breast cancer and thyroid cancer.

Patients and methods

There were 12,906 patients who were confirmed by breast cancer from January 2011 to December 2014 in Tianjin Medical University Cancer Institute and Hospital. We collected data from a review of inpatient medical records and from direct patient follow-up visits. Major inclusion criteria were as follows: female patients; age eighteen years or older; pathologic diagnosis of primary breast cancer and primary thyroid cancer. Major exclusion criteria were as follows: concurrent cancers besides breast cancer and thyroid cancer; pathological diagnosis of breast cancer or thyroid cancer which were metastasis from other cancers; incomplete medical records and patients who were lost to follow-up. Finally, a total of 52 patients who were diagnosed with breast cancer and thyroid cancer simultaneously or successively were analyzed retrospectively. And there were 26 breast cancer patients with second primary thyroid cancer. We randomly selected 144 female patients who were diagnosed with breast cancer alone as control group during the same period. For each subject

Table 2. Clinicopathological results of the 52 breast cancer patients with thyroid cancer

	BTC	TBC	*P* value
Age at breast cancer diagnosis (years)	49.0±9.2	51.9±6.5	0.826
30-39	4 (15.4%)	1 (9.2%)	
40-49	10 (38.5%)	5 (45.4%)	
50-59	10 (38.5%)	5 (45.4%)	
≥60	2 (7.6%)	0 (0)	
Time between cancers (months)	14.2±8.3	55.0±33.0	0.002
≤6	0	0	
7-12	14 (53.8%)	1 (9.1%)	
13-36	12 (46.2%)	4 (36.4%)	
37-60	0	1 (9.1%)	
61-84	0	3 (27.3%)	
≥85	0	2 (18.1%)	
Bilaterality[a]			
(+)	9 (34.6%)	0	
(-)	17 (66.4%)	11 (100%)	0.036
CLN invasion[b]			
(+)	3 (11.5%)	3 (27.3%)	
(-)	23 (88.5%)	8 (72.7%)	0.458

Values are presented as mean (range) or number (%). a. invasion of thyroid cancer. b. invasion of cervical lymph nodes due to thyroid cancer.

in the study population, we obtained the date of breast cancer diagnosis, age at both cancers diagnosis, height and weight, demographic data that including family history of tumor, menarche age, age of first pregnancy and so on. The pathological features including pathological type, tumor size, lymph nodes status, TNM stage and molecular subtype were all extracted from medical records in our center.

BTC (Breast and Thyroid Cancer) patients were defined as primary thyroid cancer occurring more than 6 months after initial primary breast cancer diagnosis. TBC (Thyroid and Breast Cancer) patients were defined as primary breast cancer occurring more than 6 months after initial primary thyroid cancer diagnosis. All breast cancer patients had received surgery, then six or eight cycles of chemotherapy, radiotherapy if necessary and hormonal therapy if estrogen receptor (ER) or progesterone receptor (PR) positive. Complete or partial thyroidectomy had been applied to thyroid cancer, with adjuvant radioiodine ablation therapy used for the residual as well as thyroid-stimulating hormone suppression. Follow-up studies comprised routine ultrasonography of chest wall and contralateral breast and cervical lymph nodes and the level of tumor marker. At one year postoperatively besides the above-mentioned tests, computed tomography (CT) of chest and mammography were performed. The length of follow-up for each patient was measured as the time from diagnosis of the breast cancer to June 2015.

Statistical analysis

For statistical methods, Pearson chi-square test and Fisher's exact tests were performed for categorical variables and the independent t-test was used for continuous variables between BTC and BC group. We also study the relevant clinical parameters in a binary logistic regression analysis. A value of $P<0.05$ (two-sided) was regarded as statistically significant. Survival differences between BCTC and BC group were assessed with log-rank test in the univariate analysis and prognostic factors were then investigated by Cox regression analysis. All analyses were performed using SPSS version 17.0.

Results

Patient characteristics

The clinicopathological features of the patients were summarized in **Table 1**. There were 196 female patients with a mean age of 51.5 years (range: 28-78). Invasive ductal carcinoma was the most common pathologic type in breast cancer (n=171, 87.2%). Her-2 expression was observed in 32 (16.3%) patients. And there were 24 (15.9%) triple negative breast cancer (TNBC) patients. Modified radical mastectomy (n=180, 91.8%) and breast conserving surgery (n=16, 8.2%) were performed in 196 breast cancer patients. Additionally, 52 (26.5%) breast cancer patients received radiotherapy (**Table 1**).

There were 26 BTC patients and 11 TBC patients, while 15 patients were diagnosed

Table 3. Clinicopathological characteristics of BTC group and BC group

	BTC group n=26 (15.3%)	BC group n=144 (84.7%)	*P* value
Age of first pregnancy (years)	26.2±3.0	24.5±2.7	0.005*
Tumor size			
≤2 cm	19 (73.1%)	62 (43.1%)	
>2 cm	7 (26.9%)	82 (56.9%)	0.005*
TNM stage of breast cancer			
Stage I	12 (46.2%)	33 (22.9%)	
Stage II	12 (46.2%)	80 (55.6%)	
Stage III	2 (7.7%)	31 (21.5%)	0.010*
Pathology of breast cancer			
Invasive ductal carcinoma	25 (96.2%)	124 (86.1%)	
Others	1 (3.8%)	20 (13.9%)	0.205
Histological grade			
I-II	20 (76.9%)	6 (23.1%)	
III	117 (81.3%)	27 (18.8%)	0.608
Estrogen status			
(+)	19 (73.1%)	117 (81.3%)	
(-)	7 (26.9%)	27 (18.8%)	0.338
Her-2 status			
(+)	7 (26.9%)	20 (14.0%)	
(-)	19 (73.1%)	123 (86.0%)	0.098
Molecular subtypes			
TNBC	4 (15.4%)	17 (11.8%)	
Non-TNBC	22 (84.6%)	127 (88.2%)	0.852
Radiotherapy			
(-)	18 (84.6%)	104 (72.2%)	
(+)	8 (15.4%)	40 (27.8%)	0.755

*Significance at 0.05 level.

with both cancers simultaneously. The pathology of thyroid cancer was all papillary carcinoma. And among 26 BTC patients, 9 (34.6%) have bilateral thyroid cancer, but none TBC patients have bilateral thyroid cancer. However, distribution of age and cervical lymph nodes involvement were similar in the BTC and TBC groups (**Table 2**).

In comparison with BC group, significant difference in first pregnancy age was witnessed in BTC group (mean age: 26.2 v.s. 24.5, P=0.012). Smaller breast tumor (≤2 centimeters 73.1% v.s. 43.1%, P=0.005) and earlier stage (TNM stage III 7.7% v.s. 21.5%, P=0.01) was observed in BTC group than in BC group. Besides, the younger mean age at breast cancer diagnosis (49.0 v.s. 52.1 years, P=0.124) and the higher ratio of HER-2 expression in BTC group than BC group (26.9% v.s. 14.0%, P=0.098) though there were both no significant difference. There were no significant differences observed in body mass index (BMI), menarche age, family history of tumor, pathological type, histological grade and molecular subtype in comparison with BTC group and BC group (**Table 3**).

The age of first pregrancy (<26 y), tumor size (>2 cm), TNM stage and Her-2 expression in breast cancer were associated with thyroid cancer (**Table 4**).

Prognosis in the BCTC group and the BC group

The mean time to follow-up after the surgery to breast cancer was 29.5±11.9 months. Of the 196 study subjects, distant metastasis of breast cancer occurred in 19 patients (9.7%) and no local recurrence or distant metastasis of thyroid cancer was observed. No patient died during the follow-up time. In BCTC group, local recurrence or distant metastasis of breast cancer occurred in 2 patients (3.8%) and in BC group, local recurrence or distant metastasis of breast cancer occurred in 17 patients (8.4%). Though we observed two separated curves in Kaplan-Meier, and a higher 3-year DFS rate in BCTC group (94.1% v.s. 84.7%), the log-rank test did not show significant difference in 3-year DFS between BCTC group and BC group (P=0.145) (**Figure 1**).

Discussion

The increased risk of second primary malignancies such as thyroid cancer after occurrence of breast cancer compared with the general population has been put forward in lots of literatures [2-4]. This suggests that a probable relationship exists between breast cancer and thyroid cancer. In the present retrospective study, 0.2% (26/12906) of breast cancer patients have developed thyroid cancer and the ratio was consistent with the results of another ret-

Table 4. Logistic regression analysis results of factors in breast cancer predicting thyroid cancer

Parameters	B	S.E.	Wald	df	Sig	Exp (B)	95.0% 95.0% C.I. for EXP (B)	
							Lower	Upper
Age of first pregrancy (>26 y)	1.577	0.537	8.621	1	0.003	4.838	1.689	13.858
Tumor size (>2 cm)	-1.572	0.538	8.538	1	0.003	0.208	0.072	0.596
Histological grade (III)	0.134	0.649	0.042	1	0.837	1.143	0.320	4.078
TNM stage of breast cancer (III)	-2.193	0.968	5.128	1	0.024	0.112	0.017	0.745
ER (+)	-0.463	0.617	0.563	1	0.453	0.629	0.188	2.110
Her-2 (+)	1.243	0.610	4.151	1	0.042	3.467	1.048	11.468
Radiotherapy (+)	0.678	0.606	1.252	1	0.263	1.970	0.601	6.459
Lymph status	0.144	0.520	0.071	1	0.781	1.155	0.417	3.204

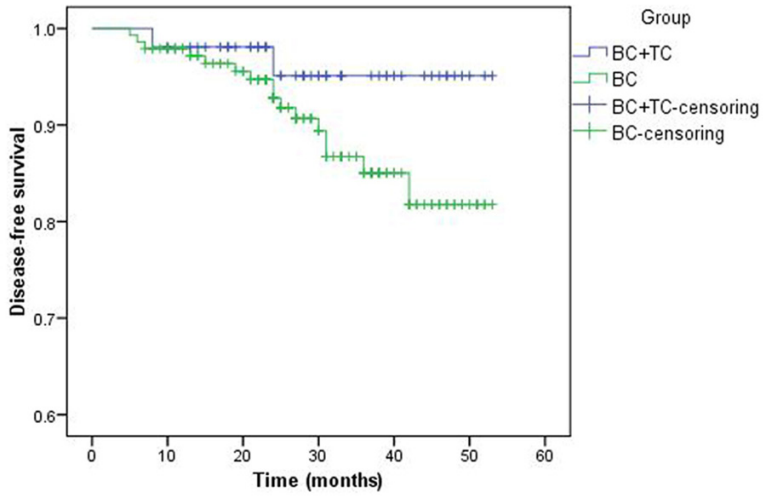

Figure 1. Kaplan-Meier analysis of 3-year DFS between BCTC group and BC gro.

rospective study of American National Cancer Institute (1526/704402=0.2%) from 1973 to 2011. But it is much lower by contrast with a prospective study that thyroid cancer is diagnosed 1.9% in breast cancer patients [11]. The different results probably due to that only part of breast cancer patients received thyroid examination in the retrospective study, but in the prospective study, all of the patients received ultrasonography screening for thyroid. And some papers have found that patients with a history of breast cancer might have greater predisposition to develop thyroid cancer especially within five years [12, 13]. In our study, we could found all breast cancer patients develop second primary thyroid cancer at or within three years from BTC group maybe confined by the short follow-up time. From the description above, the surveillance of thyroid among patients with a history of breast cancer is necessary. And it is also considerable that examine the thyroid (thyroid palpation or/and ultrasound examination) before the surgery of breast cancer.

To find out the characteristics of breast cancer patients who are predisposed to develop thyroid cancer, for the first time, we compare the data of clinicopathological features of BTC group with BC group. From the analysis, later first pregnancy age is found in BTC group. However, there was no study about the association between reproductive factors and the risk of thyroid cancer in female with a history of breast cancer. But a meta-analysis of prospective studies from Caini S et al, which included twenty-four papers, has stated that increasing age at first pregnancy/delivery (Summary relative risks (SRR) 1.56, 95% CI 1.01-2.42) is associated with thyroid cancer risk in general population [14]. The incidence of thyroid cancer in later first pregnancy age women is increased whether in general population or in breast cancer patients, but the reason is poorly understood. Caini S et al have speculated that reproductive factors may through the mediation of estrogen receptors to influence the development of thyroid cancer. In our opinion, paying more attention to thyroid if breast cancer patients are at later first pregnancy is necessary. Moreover, it seems that early stage or nonaggressive breast cancer are more likely to develop thyroid cancer in our study. So we shouldn't neglect the surveillance

of these nonaggressive breast cancer patients. Some case reports induce experts to speculate that HER-2 positive breast cancer patients may have a higher risk to develop thyroid cancer, for instance, Zeng et al have reported a metachronous HER2-positive breast cancer with thyroid cancer; Bardhan et al have reported two male patients with HER-2 positive breast cancer who also developed thyroid cancer and Gao et al have presented three cases all showing positive staining for HER-2. But our study did not find out that HER-2 expression breast cancer patients have higher risk to develop thyroid cancer. Considering the small-scale of our study, the association between HER-2 expression breast cancer and thyroid cancer need more population-based studies and prolonged follow-up time to clarify.

In all 52 BCTC patients, BTC patients are more than TBC patients. This is consistent with the meta-analysis which indicated that the risk of developing thyroid cancer after a primary breast cancer was higher than the risk of developing breast cancer as a second primary malignancy of thyroid cancer [7]. The author has made an explaination that the effects of treatment-related factors and specific pathological processes of each cancer may contribute to this phenomenon. Maybe the treatments of breast cancer, such as chemotherapy, radiotherapy, hormonal therapy influence the development of thyroid. But in our study, we did not observed an increased incidence of thyroid cancer in breast cancer patients with a history of radiotherapy. It is consistent with the literature of Huang et al who have stated that women who have received radiotherapy for breast cancer require no special surveillance for their thyroid [15]. An Indian study has also concluded that radiotherapy of breast cancer has nothing to do with the incidence of thyroid cancer subsequently [13]. According to S. de Groot et al, the thyroid function like free thyroxin (fT4) and thyroid stimulating hormone (TSH) levels has altered during chemotherapy [16]. But the subsequent development of thyroid cancer attributed to the chemotherapy-induced thyroid function alteration is powerless. Large numbers of studies show that hypothyroidism may protect against breast cancer [17-20]. In another word, high fT4 is associated with higher risk of breast cancer. And the treatments of primary thyroid cancer whether thyroidectomy or radioiodine ablation therapy blunt thyroid function. We assume this may be the reason that TBC patients are fewer than BTC patients.

Regardless of the sequence of these two cancers, the close association between breast cancer and thyroid cancer suggest the common risk factors including common environment and common gene mutation play an important role in the progress of breast cancer and thyroid cancer. The tumor suppressor gene PTEN mutation increases the risk of breast and thyroid cancer [21]. Meanwhile, CHEK2 is also found mutated in 63% (7/11) both primary breast and thyroid cancer patients [22]. Maybe there are also other common gene mutations in patients with a history of breast cancer and thyroid cancer. And they may become the targets treatment of these two cancers.

Concurrent primary cancers did not lead to poorer survival in our study, on the contrary, from the Kaplan-Meier curve it seems that patients with a history of both primary cancers were superior to those patients with breast cancer alone. But more large population-based studies are required.

In one word, thyroid examination could be considered by the clinicians in the breast cancer patients follow-up program even if patients with an early stage breast cancer. And the prognosis of patients with both cancers seems not poorer than the patients with breast cancer alone. Reproductive factors might play a role in the etiology of thyroid cancer in breast cancer patients. In view of the small-scale and limited follow-up time of our study, we could not confirm the results firmly, but this may appeal more researchers to focus on this.

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Disclosure of conflict of interest

None.

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