Submitted: 09 June, 2023 Accepted: 02 August, 2023 Published: 15 March, 2025 DOI:10.22514/ejgo.2025.037

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Thyroid function and structure variations in female breast cancer patients with diverse pathological characteristics: a retrospective single-center investigation

Yu-zhou Lai[1], Chao Tian[1,*], Nan-xi Li[2]

[1]The affiliated cancer hospital, UESTC, Sichuan Cancer Hospital, 610042 Chengdu, Sichuan, China
[2]Medical School of University of Electronic Science and Technology of China, 610054 Chengdu, Sichuan, China

***Correspondence**
hxtc2000@163.com
(Chao Tian)

Abstract

Background: This study aims to analyze the changes in thyroid structure and function in female breast cancer patients and investigate their relationship with the clinical pathological characteristics of breast cancer. **Methods**: The data of 169 patients treated at the Breast Surgery Department of Sichuan Province Cancer Hospital between December 2019 and January 2021 were assessed, and their preoperative serum thyroid function tests and thyroid ultrasound image data were collected. The patients were then grouped according to clinical pathological characteristics, such as tumor volume, and the differences in thyroid hormones, thyroid autoantibodies related to immunity, detection of thyroid nodules by ultrasound, and the Thyroid Imaging Reporting and Data System (TI-RADS) classification of the detected nodules were compared. Additionally, we analyzed the correlation of these variables with the patients' clinical pathological characteristics. **Results**: Among patients with detected thyroid nodules, significant statistical differences in the TI-RADS classification of thyroid nodules found in relation to age, estrogen receptor (ER) expression, human epidermal growth factor receptor 2 (*HER2*) expression, histological grading and lymphovascular invasion ($p < 0.05$). Furthermore, a positive correlation was observed between the TI-RADS classification level of thyroid nodules and the ER expression level ($G = 0.511$, $p < 0.001$), and a negative correlation was observed with histological grading ($G = -0.526$, $p = 0.006$). However, there is no clear correlation between age groups, *HER2* expression, lymphovascular invasion and the TI-RADS classification level ($p > 0.05$), and no significant differences found in serum thyroid hormone levels and thyroid autoantibodies among breast cancer patients with different pathological characteristics ($p > 0.05$). **Conclusions**: Newly diagnosed breast cancer patients did not show notable differences in thyroid function. However, changes in thyroid structure were observed, which correlated with certain clinical pathological characteristics used to evaluate the severity of breast cancer and formulate treatment plans.

Keywords

Breast cancer; Pathological characteristics; Thyroid nodules; Estrogen receptor; Thyroid function

1. Introduction

Breast cancer, the most common malignancy among women in China, is increasingly affecting younger women, and its incidence has been increasing annually [1, 2]. Similarly, thyroid and breast diseases are highly prevalent among women, posing a significant threat to their physical and mental well-being, as well as quality of life [3]. Although numerous studies have been conducted to explore the relationship between thyroid and breast cancer and their respective impact on the patients, substantial inconsistencies have been observed in the obtained results.

The regulation of the endocrine system is complex, influenced by hormone metabolism and diet, and characterized by hormone interactions. In the initial stages of the disease, the body's compensatory mechanisms may maintain a relatively stable state of thyroid hormones, leading to delayed manifestations and making it challenging to detect abnormalities through laboratory tests. However, changes in thyroid structure can be accurately identified in the early stages using non-invasive ultrasound, which can also help determine the nature of detected nodules. Current literature has primarily focused on examining the relationship between breast cancer and the thyroid

This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).
 ©2025 The Author(s). Published by MRE Press.

by comparing thyroid function in breast cancer patients with healthy individuals, and there has been limited emphasis on investigating alterations in thyroid structure and the correlation between thyroid function/structure and the severity of breast cancer pathology.

Based on clinical observations, we have noted that many patients, at the time of initial diagnosis, display structural abnormalities in the thyroid that are identifiable through ultrasound. Interestingly, these patients also demonstrated normal thyroid hormone levels, and their thyroid-related autoantibody expression levels were within the functional range. Therefore, we designed this study to investigate the ultrasound findings of structural changes in the thyroid among breast cancer patients and also explore the expression of thyroid hormone levels and thyroid-related autoantibodies in this patient population. To achieve this, we conducted a retrospective analysis using medical records of 169 female breast cancer patients who underwent their initial consultation at the Breast Surgery Department of Sichuan Cancer Hospital. By comparing the variations in both thyroid function and structure across different patient groups, as categorized by pathological characteristics, we established correlations between these variables and the pathological features in the patients. Overall, the findings from this study may help enhance healthcare professionals' awareness about the significance of conducting thorough thyroid examinations during the diagnosis, treatment and follow-up processes of breast cancer patients.

2. Materials and methods

2.1 General information

The data of 169 female patients diagnosed with infiltrative breast cancer between December 2019 and January 2021 at the Department of Breast Surgery (Sichuan Cancer Hospital, Sichuan, China) were retrieved and assessed. They were treatment naive breast cancer patients with no previous thyroid disease history, had not been prescribed hormone medications or received iodine-containing contrast agents within the past six months before this study, none had undergone radiation therapy, chemotherapy or endocrine therapy before their surgery, and all had comprehensive thyroid test records prior to the initiation of their treatment. Of enrolled cases, 80 were classified as post-menopausal and 79 as pre-menopausal.

Following the guidelines outlined in the "Chinese consensus guidelines for breast cancer in young women: clinical practice and fertility preservation" [4], 15 patients were classified as young breast cancer patients (age, $\leq$35 years old) and the remaining 154 as older breast cancer patients (age, >35 years old). The average age of the patients was 50.8 $\pm$ 3.5 years (range, 77 to 30 years old).

The pathological data were obtained from the Pathology Department of Sichuan Cancer Hospital. Tumor size was classified as T1–T4 according to the Cancer Staging Manual of the 8th edition of the American Joint Committee on Cancer (AJCC) [5]. Immunohistochemical staining was conducted on tumor tissue specimens obtained from surgeries, and based on the Ki-67 staining results, they were divided into three categories: low expression ($\leq$14%), moderate expression (15%–30%), and high expression (>30%), following the 2022 standards outlined in the Breast Cancer Diagnosis and Treatment Guidelines of the Chinese Society of Clinical Oncology [6]. The expression of estrogen and progesterone receptors was evaluated following the 2020 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines [7], with a threshold of $\geq$1% for positive immunohistochemistry of estrogen receptor (ER)/progesterone receptor (PR). This study reported positive detection results based on the staining intensity and percentage of tumor cells, with "+" symbol used to indicate positive intensity. The evaluation of human epidermal growth factor receptor 2 (*HER2*) detection results was based on the 2019 *HER2* Detection Guidelines [8] and the 2021 Consensus on Clinical Diagnosis and Treatment of *HER2*-Positive Breast Cancer [9]. Due to insufficient evidence that patients with low *HER2* expression can benefit from current antibody-drug conjugate treatments, patients with negative or low *HER2* expression in this study were defined as non-amplified *HER2*, while the others were defined as amplified *HER2*. Histological grading was performed using the Nottingham grading system [10].

2.2 Observation indicators and evaluation standards

The thyroid hormone and autoantibody test results were obtained from the Nuclear Medicine Department of Sichuan Cancer Hospital. Blood samples were collected in the morning before surgery under basal conditions. The reference values for the hospital's Nuclear Medicine Department tests were as follows: free triiodothyronine (FT3): 2.2–4.2 pg/mL; free thyroxine (FT4): 0.8–1.7 ng/dL; thyroid stimulating hormone (TSH): 0.3–5.0 mIU/L; thyroid peroxidase antibodies (TPOAb): 1–16 IU/mL; thyroglobulin antibodies (TGAb): 5–100 IU/mL. Based on the test reference range, TPOAb >16 IU/mL was considered positive, and TGAb $\geq$5 IU/mL was considered positive in this study.

The thyroid ultrasound imaging data were obtained from the Ultrasound Department of Sichuan Cancer Hospital, among which 92 cases had no nodules, while 77 cases had nodules on ultrasound. The nodules were classified into four categories (1, 2, 3 or 4a) based on the 2020 Chinese Guideline for Thyroid Nodule Ultrasound Malignancy Risk Stratification: C-TIRADS [11]. For multiple nodules with different classifications, the highest category was recorded.

2.3 Statistical analysis

All data were assessed using the Statistical Product and Service Solutions (SPSS, version 21.0, International Business Machines Corporation, Armonk, NY, USA) software. Qualitative data, such as the thyroid ultrasound imaging data (*i.e.*, presence or absence of thyroid nodules), the TI-RADS classification of the nodules, and the thyroid autoantibody test results (positive/negative), are presented as absolute numbers. The differences between variables were analyzed using the Chi-square test when comparing two groups or unordered multiple groups. The Kruskal-Wallis H rank sum test was used for ordinal multiple groups. Correlation analysis of variables was performed using Pearson's correlation coefficient

for unordered categorical variables and the Gammer method for ordered categorical variables. The results of the thyroid hormone (quantitative data) are expressed as mean ± standard deviation. The *t*-test was used to analyze differences between two groups, while one-way analysis of variance (ANOVA) was used for comparisons among multiple groups. A significance level of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Thyroid ultrasound findings in breast cancer patients

The results indicated no significant difference in the presence of thyroid nodules detected by ultrasound among breast cancer patients (Table 1). However, among the breast cancer patients with detected thyroid nodules, significant differences were observed in the TI-RADS classification based on different pathological features (Table 2). The difference in the TI-RADS classification of thyroid nodules among patients with different ER expressions was found to be statistically significant ($H = 12.165$, $p = 0.007$). Moreover, a positive correlation was observed between the level of ER expression and the TI-RADS classification of thyroid nodules, indicating that higher ER expression was associated with a higher TI-RADS classification level ($G = 0.511$, $p < 0.001$). Additionally, there was a statistically significant difference in the TI-RADS classification of thyroid nodules among breast cancer patients with different histological grades ($H = 6.018$, $p = 0.049$). Specifically, higher histological grades were associated with lower TI-RADS classification levels of the detected thyroid nodules ($G = -0.526$, $p = 0.006$). Regarding age groups, *HER2* expression and lymphovascular invasion status, we observed statistically significant differences in the TI-RADS classification of thyroid nodules ($p < 0.05$). However, no clear correlation was observed between age groups, *HER2* expression, lymphovascular invasion, and the TI-RADS classification level (Table 3, Figs. 1,2).

3.2 Serum thyroid hormone levels in breast cancer patients

When divided into groups based on pathological features, the average hormone levels of the included cases were found to be within the normal reference range, and we found no statistically significant difference in the thyroid hormone levels among breast cancer patients with different pathological features ($p > 0.05$) (Table 4).

3.3 Expression of thyroid autoantibodies in the serum of breast cancer patients

There was no statistically significant difference in the expression of serum TPOAb and TGAb levels in breast cancer patients grouped based on different pathological features ($p > 0.05$) (Table 5).

4. Discussion

The breasts and thyroids are hormone-responsive organs regulated by the hypothalamic-pituitary axis. The growth of transformed breast tissue cells can still be influenced by endocrine regulation due to the differential expression of hormone receptors. Several studies have suggested the possibility of abnormal thyroid function in influencing breast cancer progression. It was previously proposed that hypothyroidism might benefit breast cancer patients in terms of prognosis [12]. In this study, we explored the thyroid function of breast cancer patients. Even in patients with thyroid hormone levels within the normal range, we observed that patients with indicators of a good prognosis (*i.e.*, ER and PR positive, *HER2* negative, without lymph node metastasis, without lymphovascular invasion and lower histological grades) had lower levels of FT3 and FT4, as well as higher levels of TSH, compared to patients with poorer prognostic indicators. However, it is important to note that the lack of statistical significance might have been attributed to the small sample size and the retrospective nature of this study.

However, the observed correlation between changes in thyroid structure and the severity of breast cancer highlights the need for further investigation in this area. Notably, we observed significant differences in the TI-RADS classification of thyroid nodules among patients with different pathological features. The TI-RADS classification system is a well-established method that stratifies thyroid nodules based on their ultrasound characteristics, with higher TI-RADS classifications typically indicating an increased risk of malignancy.

The results of our study suggest that while there was no statistically significant difference in the detection rate of thyroid nodules among different age groups, there were variations in the TI-RADS classification of thyroid nodules in different age groups. As individuals age, various factors such as degenerative changes in thyroid function, the presence of chronic underlying diseases, onset of metabolic syndrome and accumulation of risk factors such as ionizing radiation gradually surpass the threshold for structural changes in the thyroid. Consequently, there is an increased incidence of abnormal proliferation of thyroid cells and the formation of nodules [13]. Furthermore, we hypothesize that in patients with breast cancer, the abnormal proliferation of cancer cells may disrupt the secretion rhythm of hormones, particularly estrogen, and the extent of disruption in hormone rhythms may differ among patients of different ages. Dysregulated hormone levels could lead to varying degrees of abnormal proliferation and differentiation of thyroid cells, resulting in the formation of thyroid nodules with distinct biological morphologies. However, it is important to note that further exploration is needed to fully understand the potential correlation between these factors.

Currently, the primary molecular biological indicators tested for breast cancer include ER, PR, *HER2* and Ki-67. Within the ER category, there are two subtypes: ERα and ERβ, which play different roles within cells. Both thyroid and breast tissues contain ERα (promotes cancer cell growth) and ERβ (inhibits cancer cell growth) [14, 15]. In normal breast epithelial cells, ER expression and other hormone receptors regulate cell growth and proliferation through the endocrine system.

TABLE 1. Presence of thyroid nodules detected by ultrasound in breast cancer patients with different pathological features.

Pathological Features	Thyroid Nodules		χ^2/H	*p*
	Not Detected	Detected		
Age				
≤35 years old	10	5	0.992	0.319
>35 years old	82	72		
Tumor diameter				
T1	39	28	6.083	0.108
T2	48	43		
T3	5	2		
T4	0	4		
Ki-67				
≤14%	14	13	0.890	0.641
15%–30%	26	26		
>30%	52	38		
Estrogen receptor				
−	37	20	4.709	0.194
+	9	6		
++	7	9		
+++	39	42		
Progesterone receptor				
−	39	26	4.555	0.207
+	23	16		
++	6	12		
+++	24	23		
HER2				
Unamplified	62	46	1.064	0.302
Amplified	30	31		
Lymph node metastasis				
Yes	51	40	0.205	0.651
No	41	37		
Histological grades				
I	2	5	4.156	0.125
II	51	49		
III	39	23		
Lymphovascular invasion				
Yes	31	32	1.108	0.292
No	61	45		
Complicated with breast ductal carcinoma *in situ*				
Yes	34	26	0.186	0.666
No	58	51		

HER2: human epidermal growth factor receptor 2; −: No detectable nuclear staining or staining in <1% of tumor cells. Considered that the tumor is negative for ER or PR expression; +: Nuclear staining in 1%–10% of tumor cells with weak intensity. Considered weakly positive for ER or PR; ++: Nuclear staining in 70%–80% of tumor cells with moderate intensity. Considered moderate positivity for ER or PR; +++: Nuclear staining in 90%–100% of tumor cells with strong intensity. Considered strong positivity for ER or PR.

TABLE 2. TI-RADS classification of thyroid nodules in breast cancer patients with different pathological features.

Pathological Features	TI-RADS Classification				χ^2/H	*p*
	1	2	3	4a		
Age						
≤35 years old	1	2	1	1	16.857	0.001
>35 years old	0	14	46	12		
Tumor diameter						
T1	0	6	16	6	2.226	0.527
T2	1	9	28	5		
T3	0	0	1	1		
T4	0	1	2	1		
Ki-67						
≤14%	0	3	9	1	0.982	0.612
15%–30%	0	4	17	5		
>30%	1	9	21	7		
Estrogen receptor						
−	1	5	14	0	12.165	0.007
+	0	2	3	1		
++	0	5	3	1		
+++	0	4	27	11		
Progesterone receptor						
−	1	7	16	2	5.703	0.127
+	0	3	10	3		
++	0	3	8	1		
+++	0	3	13	7		
HER2						
Unamplified	0	6	30	10	5.971	0.015
Amplified	1	10	17	3		
Lymph node metastasis						
Yes	1	6	26	7	0.510	0.475
No	0	10	21	6		
Histological grades						
I	0	1	2	2	6.018	0.049
II	0	7	32	10		
III	1	8	13	1		
Lymphovascular invasion						
Yes	1	3	20	8	4.044	0.044
No	0	13	27	5		
Complicated with breast ductal carcinoma *in situ*						
Yes	0	6	17	3	0.338	0.561
No	1	10	30	10		

TI-RADS: Thyroid imaging reporting and data system; HER2: human epidermal growth factor receptor 2; −: No detectable nuclear staining or staining in <1% of tumor cells. Considered that the tumor is negative for ER or PR expression; +: Nuclear staining in 1%–10% of tumor cells with weak intensity. Considered weakly positive for ER or PR; ++: Nuclear staining in 70%–80% of tumor cells with moderate intensity. Considered moderate positivity for ER or PR; +++: Nuclear staining in 90%–100% of tumor cells with strong intensity. Considered strong positivity for ER or PR.

TABLE 3. Correlation between pathological features of breast cancer patients and TI-RADS classification of thyroid nodules.

Pathological Features	TI-RADS Classification				G/*r*	*p*
	1	2	3	4a		
Age						
≤35 years old	1	2	1	1	0.460	0.305
>35 years old	0	14	46	12		
Estrogen receptor						
−	1	5	14	0		
+	0	2	3	1	0.511	<0.001
++	0	5	3	1		
+++	0	4	27	11		
HER2						
Unamplified	0	6	30	10	0.292	0.067
Amplified	1	10	17	3		
Histological grades						
I	0	1	2	2		
II	0	7	32	10	−0.526	0.006
III	1	8	13	1		
Lymphovascular invasion						
Yes	1	3	20	8	0.288	0.072
No	0	13	27	5		

TI-RADS: Thyroid imaging reporting and data system; HER2: human epidermal growth factor receptor 2; −: No detectable nuclear staining or staining in <1% of tumor cells. Considered that the tumor is negative for ER or PR expression; +: Nuclear staining in 1%–10% of tumor cells with weak intensity. Considered weakly positive for ER or PR; ++: Nuclear staining in 70%–80% of tumor cells with moderate intensity. Considered moderate positivity for ER or PR; +++: Nuclear staining in 90%–100% of tumor cells with strong intensity. Considered strong positivity for ER or PR.

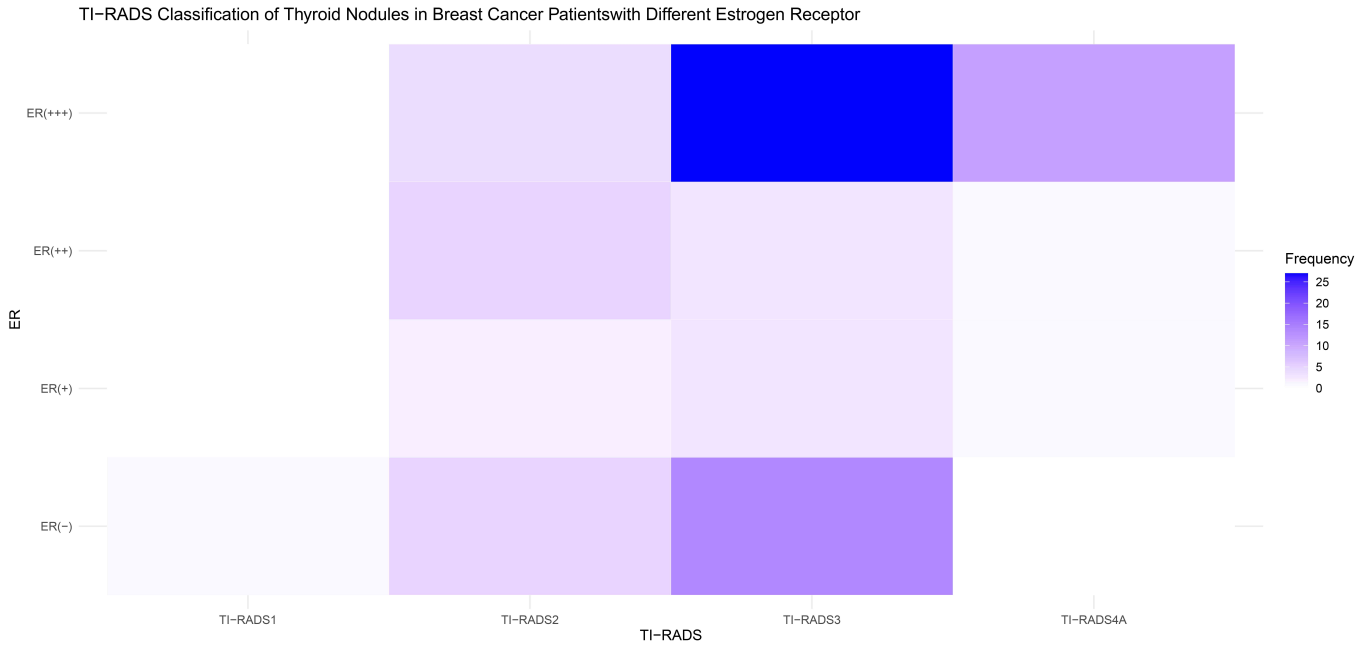

FIGURE 1. TI-RADS classification of thyroid nodules in breast cancer patients with different estrogen receptor. TI-RADS: thyroid imaging reporting and data system; ER: estrogen receptor.

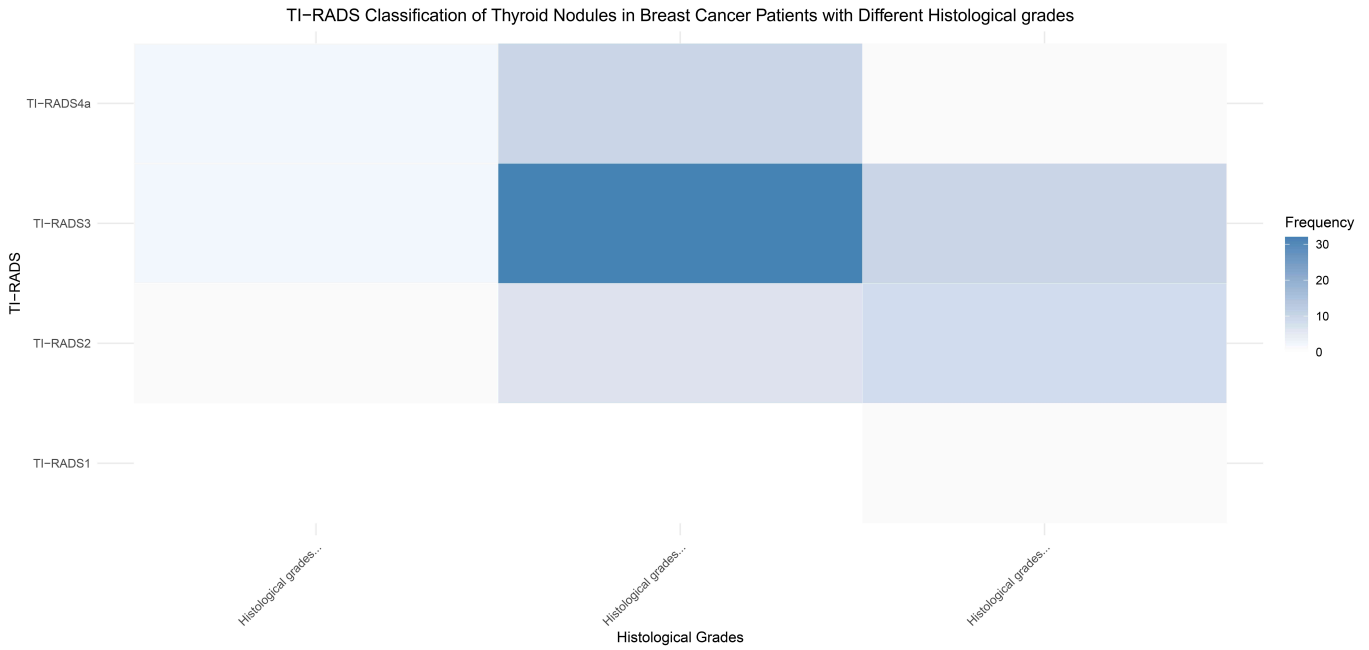

FIGURE 2. TI-RADS classification of thyroid nodules in breast cancer patients with different histological grades. TI-RADS: thyroid imaging reporting and data system.

TABLE 4. FT3, FT4 and TSH levels in breast cancer patients with different pathological features.

Pathological Features	n	FT3 (pg/mL)	FT4 (ng/dL)	TSH (mIU/L)
Age				
≤35 years old	15	2.67 ± 0.209	1.19 ± 0.179	2.67 ± 1.059
>35 years old	154	2.65 ± 0.378	1.14 ± 0.177	2.57 ± 2.310
t/*F*		0.148	1.015	0.166
p		0.883	0.312	0.868
Tumor diameter				
T1	67	2.63 ± 0.229	1.14 ± 0.160	2.72 ± 2.350
T2	91	2.67 ± 0.446	1.17 ± 0.180	2.44 ± 2.210
T3	7	2.58 ± 0.297	0.98 ± 0.140	2.76 ± 1.620
T4	4	2.71 ± 0.388	1.10 ± 0.220	2.86 ± 1.810
t/*F*		0.319	2.610	0.240
p		0.812	0.053	0.868
Ki-67				
≤14%	27	2.64 ± 0.285	1.11 ± 0.140	2.18 ± 1.270
15%–30%	52	2.62 ± 0.282	1.15 ± 0.220	2.50 ± 2.280
>30%	90	2.68 ± 0.427	1.15 ± 0.160	2.74 ± 2.410
t/*F*		0.476	0.560	0.715
p		0.622	0.573	0.491
Estrogen receptor				
−	57	2.71 ± 0.512	1.14 ± 0.175	2.55 ± 2.578
+	15	2.62 ± 0.382	1.07 ± 0.137	2.94 ± 2.366
++	16	2.58 ± 0.207	1.10 ± 0.169	2.46 ± 1.833
+++	81	2.63 ± 0.245	1.17 ± 0.183	2.55 ± 2.029
t/*F*		0.844	4.398	0.147
p		0.472	0.222	0.931

TABLE 4. Continued.

Pathological Features	n	FT3 (pg/mL)	FT4 (ng/dL)	TSH (mIU/L)
Progesterone receptor				
−	65	2.72 ± 0.488	1.16 ± 0.168	2.61 ± 2.632
+	39	2.62 ± 0.275	1.11 ± 0.163	2.33 ± 1.175
++	18	2.55 ± 0.261	1.18 ± 0.265	3.09 ± 2.131
+++	47	2.63 ± 0.243	1.15 ± 0.161	2.55 ± 2.342
t/*F*		1.270	1.830	0.482
p		0.286	0.608	0.695
HER2				
Unamplified	108	2.62 ± 0.262	1.13 ± 0.167	2.66 ± 2.474
Amplified	61	2.71 ± 0.497	1.17 ± 0.193	2.43 ± 1.710
t/*F*		−1.654	−1.216	0.667
p		0.100	0.226	0.506
Lymph node metastasis				
Yes	91	2.70 ± 0.426	1.15 ± 0.168	2.43 ± 1.761
No	78	2.60 ± 0.274	1.14 ± 0.188	2.75 ± 2.671
t/*F*		1.610	0.297	−0.920
p		0.109	0.767	0.359
Histological grades				
I	7	2.55 ± 0.280	1.19 ± 0.130	1.72 ± 0.79
II	100	2.65 ± 0.407	1.13 ± 0.180	2.61 ± 2.31
III	62	2.67 ± 0.301	1.16 ± 0.180	2.63 ± 2.21
t/*F*		0.332	0.505	0.538
p		0.718	0.605	0.585
Lymphovascular invasion				
Yes	63	2.71 ± 0.493	1.15 ± 0.192	2.53 ± 2.514
No	106	2.62 ± 0.260	1.14 ± 0.169	2.61 ± 2.048
t/*F*		1.599	0.442	−0.211
p		0.112	0.659	0.833
Complicated with breast ductal carcinoma *in situ*				
Yes	60	2.62 ± 0.298	1.14 ± 0.182	2.57 ± 1.818
No	109	2.67 ± 0.399	1.15 ± 0.175	2.58 ± 2.430
t/*F*		0.772	−0.128	−0.033
p		0.491	0.898	0.973

FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone; HER2: human epidermal growth factor receptor 2; −: No detectable nuclear staining or staining in <1% of tumor cells. Considered that the tumor is negative for ER or PR expression; +: Nuclear staining in 1%–10% of tumor cells with weak intensity. Considered weakly positive for ER or PR; ++: Nuclear staining in 70%–80% of tumor cells with moderate intensity. Considered moderate positivity for ER or PR; +++: Nuclear staining in 90%–100% of tumor cells with strong intensity. Considered strong positivity for ER or PR.

Breast cancer cells exhibit varying degrees of ER deficiency compared to normal cells. The remaining ER allows hormone control over the growth and proliferation of cancer cells, and this mechanism is utilized in cancer treatment by reducing estrogen levels through medication. Studies have demonstrated that the expression of ERα gradually increases in breast cancer patients while the expression of ERβ gradually decreases [16]. It is speculated that the immunohistochemistry-detected expression of ER in tumor tissue primarily represents the α subtype, while the β subtype is relatively deficient. Studies examining thyroid diseases have revealed that female patients with thyroid lesions exhibit lower ERβ expression in thyroid tissue than in the control group, with this downregulation in ERβ expression being more pronounced in malignant thyroid lesions [17, 18]. Based on these reports, it could be hypothesized that higher classifications according to TI-RADS might

TABLE 5. Expression of TPOAb and TGAb expression in breast cancer patients with different pathological features.

Pathological Features	TPOAb		χ^2/H	*p*	TGAb		χ^2/H	*p*
	Positive	Negative			Positive	Negative		
Age								
≤35 years old	5	10	0.540	0.462	3	12	2.370	0.124
>35 years old	38	116			62	92		
Tumor diameter								
T1	19	48	2.691	0.456	21	46	3.701	0.303
T2	23	68			41	50		
T3	0	7			2	5		
T4	1	3			1	3		
Ki-67								
≤14%	7	20	0.974	0.614	11	16	0.356	0.837
15%–30%	10	42			20	32		
>30%	26	64			34	56		
Estrogen receptor								
−	15	42	2.130	0.546	22	35	0.272	0.965
+	6	9			6	9		
++	4	12			7	9		
+++	18	63			30	51		
Progesterone receptor								
−	19	46	1.139	0.768	25	40	0.379	0.945
+	8	31			14	25		
++	5	13			8	10		
+++	11	36			18	29		
HER2								
Unamplified	24	84	1.637	0.201	36	72	3.325	0.068
Amplified	19	42			29	32		
Lymph node metastasis								
Yes	20	71	1.248	0.264	39	52	1.610	0.205
No	23	55			26	52		
Histological grades								
I	3	4	1.180	0.554	3	4	0.238	0.888
II	25	75			37	63		
III	15	47			25	37		
Lymphovascular invasion								
Yes	19	44	1.177	0.278	22	41	0.532	0.466
No	24	82			43	63		
Complicated with breast ductal carcinoma *in situ*								
Yes	14	46	0.218	0.640	27	33	1.680	0.195
No	29	80			38	71		

TPOAb: thyroid peroxidase antibodies; TGAb: thyroglobulin antibodies; HER2: human epidermal growth factor receptor 2; −: No detectable nuclear staining or staining in <1% of tumor cells. Considered that the tumor is negative for ER or PR expression; +: Nuclear staining in 1%–10% of tumor cells with weak intensity. Considered weakly positive for ER or PR; ++: Nuclear staining in 70%–80% of tumor cells with moderate intensity. Considered moderate positivity for ER or PR; +++: Nuclear staining in 90%–100% of tumor cells with strong intensity. Considered strong positivity for ER or PR.

be associated with lower ERβ expression. In this present study, breast cancer patients with higher levels of ER expression were also observed to exhibit higher-level classified thyroid nodules, suggesting that these patients might have lower ERβ expression in various tissues, and individual variations could be related to the expression status and level of ERα.

Despite the ongoing debate regarding the impact of ER expression levels and HR subtype expression levels on the efficacy of endocrine therapy, it is evident that patients with different hormone receptor expressions exhibit varying sensitivities to anti-estrogen treatment [16]. Currently, there is no standardized definition for high and low levels of HR expression in clinical practice, and there is a lack of specific qualitative or objective quantification methods for receptor subtype expression in breast tumor tissues. In this context, the observed correlation between higher ER levels and higher TI-RADS classifications of thyroid nodules seems intriguing. The integration of these findings with the results of thyroid examinations could contribute to a more precise endocrine treatment plan for hormone receptor-positive breast cancer patients and may also guide the selection of more specific anti-hormone receptor drugs for personalized and tailored therapeutic approaches.

HER2 has long been recognized as an important prognostic factor in breast cancer and plays a crucial role in guiding treatment decisions, with *HER2* positivity considered an independent risk factor for poor prognosis [19]. Both domestic and international studies have demonstrated *HER2* expression in thyroid tumors, with a significantly higher positive rate observed in malignant thyroid tumors than in benign lesions. Moreover, the high positive *HER2* expression rate has been associated with the degree of malignancy [20–22]. Studies on synchronous breast and thyroid cancer have reported data supporting a positive correlation between *HER2* expression in these two types of cancer [23]. However, there is limited research on the impact of *HER2* on the development of benign thyroid lesions. Although no evident correlation was observed, our study found differences in the TI-RADS classification of detected nodules between *HER2*-negative and *HER2*-positive patients. While this requires further validation through comprehensive studies, it suggests that examining thyroid morphological changes could contribute to the development of new prognostic tools and targeted therapies for HER2-positive patients. As previously mentioned, the benefit of current antibody-conjugate drug-targeted therapy for patients classified as having low *HER2* expression according to current evaluation criteria remains controversial. Thus, incorporating the evaluation of thyroid status may offer new insights for implementing more precise therapeutic strategies for this specific group of patients.

In this study, thyroid nodules detected in patients with high-grade breast cancer demonstrated lower TI-RADS classification levels. Histological grading of invasive breast cancer is based on prognosis-related parameters, with higher grades indicating poorer tumor cell morphology. The underlying reason for this observation may involve specific signaling molecules that exert opposing effects on the regulation of differentiation in breast and thyroid tissues. For example, recent breast cancer research has highlighted the role of hypoxia-inducible factor-2α (HIF-2α) in tumor tissue differentiation. It has been reported that patients with high expression of HIF-2α have poor breast tumor tissue differentiation [24]. However, HIF-2α also plays an inhibitory role in the progression of malignant thyroid tumors [25]. We hypothesized that high expression of certain substances in patients with high-grade breast cancer might suppress the transformation of abnormally proliferating thyroid cells towards a malignant biological morphology, leading to a reduced malignant risk of thyroid nodules and lower TI-RADS classification. The exact mechanism that links the biological behavior of breast cancer and thyroid nodules remains unclear. However, the observed connection between these two entities may offer a novel direction for evaluating the prognosis of breast cancer patients with coexisting thyroid diseases.

This study reveals a difference in the TI-RADS classification of thyroid nodules between patients with lymphovascular invasion and those with non-invasive breast cancer. Lymphovascular invasion is a significant risk factor for poor prognosis in various types of cancer. In breast cancer, lymphovascular invasion is closely associated with residual or recurrent metastasis following radical mastectomy [26, 27]. Some studies suggest that lymphovascular invasion is an independent adverse prognostic indicator, separate from other pathological factors, and efforts have been made to systematically stratify breast cancer patients with lymphovascular invasion using various approaches [28–31]. Currently, the gold standard for confirming lymphovascular invasion status is postoperative pathological examination of resected lesions. Preoperative prediction of tumor lymphovascular invasion mainly relies on features observed in breast magnetic resonance imaging [32, 33]. By examining the thyroid and conducting further prospective studies to validate the association between thyroid status and lymphovascular invasion, we may identify additional avenues to enhance the accuracy of preoperative predictions of lymphovascular invasion in breast cancer patients, which may in turn assist in clinical decision-making regarding neoadjuvant therapy before breast cancer surgery.

Our research findings highlight the association between the nature of thyroid nodules detected in breast cancer patients and certain clinical characteristics that indicate the severity and prognosis of the disease and underscore the importance of conducting comprehensive thyroid examinations in breast cancer patients. By monitoring structural changes in the thyroid, clinicians can gain insights into the severity of breast cancer and develop more personalized and precise treatment plans. Regular thyroid function tests and color Doppler ultrasound assessments during breast disease treatment can be beneficial. When thyroid changes are detected in breast cancer patients, additional evaluations can be performed to promptly assess the severity of the disease, predict its progression status, and initiate timely interventions.

However, it is important to acknowledge the limitations of our study. The data used were derived from a single center, and the representativeness of the data might have been influenced by the clinical diagnosis and treatment capabilities of our hospital. Additionally, the sample size was relatively small, and the study's retrospective nature prevented us from accurately determining the sequence of occurrence and progression of

breast cancer and thyroid structural changes. Therefore, it is crucial to validate our observed correlation through large-sample, multicenter prospective studies to strengthen the reliability and generalizability of our findings.

5. Conclusions

Newly diagnosed breast cancer patients did not exhibit significant differences in thyroid function. However, variations were observed in thyroid structure changes, which correlated with certain clinical pathological characteristics used to assess the severity of breast cancer and guide treatment decisions.

AVAILABILITY OF DATA AND MATERIALS

The data used and analyzed in the current study are available from the corresponding authors upon reasonable request.

AUTHOR CONTRIBUTIONS

YZL—designed the research study, collected data and drafted the manuscript. YZL and CT—analyzed, interpreted all the results, substantial revisions and to produce the final manuscript. NXL—helped with data collection and cross-check. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for the study was obtained from the Research Ethics Committee of the Sichuan Cancer Hospital. Formal ethical approval document with reference number was not required as this study was a retrospective study, and every patient besides those included in the criteria in the study underwent regular case handling so all the data analyzed were part of routine diagnostics and treatment, not additional procedures specifically for the study. The data used are anonymized and de-identified. Additional informed consent was therefore waived.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This study received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Zhang X, Dong XP, Guan YJ, Ren M, Guo DL, He YT. Research progress on epidemiological trend and risk factors of female breast cancer. Cancer Research on Prevention and Treatment. 2021; 48: 87–92. (In Chinese)

[2] Wang B, Li YZ. Treatment and ethical thinking of fertility preservation in young breast cancer patients. Chinese Medical Ethics. 2021; 34: 88–92. (In Chinese)

[3] Gago-Dominguez M, Castelao JE. Role of lipid peroxidation and oxidative stress in the association between thyroid diseases and breast cancer. Critical Reviews in Oncology/Hematology. 2008; 68: 107–114.

[4] Expert Consensus Committee on diagnosis, Treatment and fertility management of young breast cancer in China. Chinese consensus guidelines for breast cancer in young women: clinical practice and fertility preservation. Chinese Journal of Oncology. 2019; 41: 486–495. (In Chinese)

[5] Zhou B, Ji K, Xin L, Zhang H, Xu L, Li T, *et al*. Updates and interpretations of the 8th edition of AJCC breast cancer staging system. Chinese Journal of Practical Surgery. 2017; 37: 10–14. (In Chinese)

[6] Chinese Society of Clinical Oncology Guidelines Working Committee. Breast cancer diagnosis and treatment guidelines of Chinese society of clinical oncology. People's Medical Publishing House: Beijing. 2022.

[7] Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, *et al*. Her2-low breast cancer: pathological and clinical landscape. Journal of Clinical Oncology. 2020; 38: 1951–1962.

[8] Guidelines for HER2 Testing in Breast Cancer (2019 Edition) Writing Group. Guideline for HER2 detection in breast cancer, the 2019 version. Chinese Journal of Pathology. 2019; 48: 169–175. (In Chinese)

[9] Breast Cancer Expert Committee of Chinese Society of Clinical Oncology, Breast Cancer Professional Committee of Chinese Anti-Cancer Association. Expert consensus on clinical diagnosis and treatment of HER2-positive breast cancer, the 2019 version. National Medical Journal of China. 2021; 101: 1226–1231. (In Chinese)

[10] Mei F, Liu JY, Xue WC. Histological grading of invasive breast carcinoma: Nottingham histological grading system. Chinese Journal of Pathology. 2019; 48: 659–664. (In Chinese)

[11] Superficial Organ and Vascular Study Group of Ultrasound Medical Branch of Chinese Medical Association, China Thyroid and Breast Ultrasound Artificial Intelligence Alliance. 2020 Chinese guidelines for ultrasound malignancy risk stratification of thyroid nodules: the C-TIRADS. Chinese Journal of Ultrasonography. 2021; 30: 185–200. (In Chinese)

[12] Herc bergs A. Hypothyroidism and tumor regression. The New England Journal of Medicine. 1988; 319: 1351–1352.

[13] Li Z, Feng F, Shen CW, Abudula A. Analysis of the detection rate of thyroid nodule and related risk factors of health check-up of women in Mingdong Hospital. Journal of Ningde Teachers College. 2022; 34: 288–294,321. (In Chinese)

[14] Gong Z, Yang S, Wei M, Vlantis AC, Chan JYK, van CA, *et al*. The isoforms of estrogen receptor alpha and beta in thyroid cancer. Frontiers in Oncology. 2022; 12: 916804.

[15] Kim YA, Kim YA, Cho SW, Song YS, Min HS, Park IA, *et al*. Increased expression of thyroid hormone receptor alpha and estrogen receptor alpha in breast cancer associated with thyroid cancer. European Journal of Surgical Oncology. 2021; 47: 1316–1323.

[16] Zhao J, Li J, Feng J. Research progress on the role of deubiquitinating enzyme in ER-positive breast cancer. Journal of Hubei University of Medicine. 2022; 41: 316–319. (In Chinese)

[17] Dong S, Song XS, Pang L, Liu J. Expression of sex hormones and their receptors in female patients with different types of thyroid nodules. Chinese Journal of Endocrine Surgery. 2017; 11: 29–33. (In Chinese)

[18] Xu L, Gou X, Yang J, Jiang R, Jiang X, Chen GG, *et al*. Methylation of ERβ 5′-untranslated region attenuates its inhibitory effect on ERα gene transcription and promotes the initiation and progression of papillary thyroid cancer. The FASEB Journal. 2021; 35: e21516.

[19] Wilson FR, Coombes ME, Wylie Q, Yurchenko M, Brezden-Masley C, Hutton B, *et al*. Herceptin® (trastuzumab) in HER2-positive early breast cancer: protocol for a systematic review and cumulative network meta-analysis. Systematic Reviews. 2017; 6: 196.

[20] Zhan S, Wang T, Li J, Zhu H, Ge W, Li J. Asporin interacts with HER2 to promote thyroid cancer metastasis via the MAPK/EMT signaling pathway. Frontiers in Oncology. 2022; 12: 762180.

[21] Dai YJ, Qiu YB, Jiang R, Xu M, Zhao L, Chen GG, *et al*. Concomitant high expression of ERα36, EGFR and HER2 is associated with aggressive behaviors of papillary thyroid carcinomas. Scientific Reports. 2017; 7: 12279.

[22] Ren YX, Liao M, Yang J, Wang XL, Li XJ. Expression and clinical significance of ER and HER-2 in papillary thyroid cancer. Journal of Kunming Medical University. 2020; 41: 43–48. (In Chinese)
[23] Ren YX, Liao M, Yang J, Wang XL, Li XJ. Expression and clinical pathological significance of ER, HER-2 in thyroid papillary carcinoma with breast cancer. Proceedings of the 2019 China Cancer Congress. Chongqing. 16 August 2019. China Anticancer Association: Chongqing. 2019.
[24] Bai J, Chen WB, Zhang XY, Kang XN, Jin LJ, Zhang H, *et al*. HIF-2α regulates CD44 to promote cancer stem cell activation in triple-negative breast cancer via PI3K/AKT/mTOR signaling. World Journal of Stem Cells. 2020; 12: 87–99.
[25] Zhang R, Zhao J, Zhao L. EPAS1/HIF-2α acts as an unanticipated tumor-suppressive role in papillary thyroid carcinoma. International Journal of General Medicine. 2023; 16: 2165–2174.
[26] Mori N, Mugikura S, Takasawa C, Miyashita M, Shimauchi A, Ota H, *et al*. Peritumoral apparent diffusion coefficients for prediction of lymphovascular invasion in clinically node-negative invasive breast cancer. European Radiology. 2016; 26: 331–339.
[27] Wang CN, Wu XY, Lin XL, Lin ZF, Feng R, Wang JB. Relationship between HPK1, PI3K expression and 5-year prognosis of patients with breast cancer after radical mastectomy. Journal of Clinical and Experimental Medicine. 2022; 21: 1286–1290. (In Chinese)
[28] Zhang S, Zhang D, Gong M, Wen L, Liao C, Zou L. High lymphatic vessel density and presence of lymphovascular invasion both predict poor prognosis in breast cancer. BMC Cancer. 2017; 17: 335.
[29] Zhong YM, Tong F, Shen J. Lympho-vascular invasion impacts the prognosis in breast-conserving surgery: a systematic review and meta-analysis. BMC Cancer. 2022; 22: 102.
[30] Chen JW, Li J, Ma SM, Wu M. Correlation analysis between axillary lymph node metastasis and preoperative MRI as well as clinicopathological features in early invasive breast cancer. Journal of China Clinic Medical Imaging. 2020; 31: 618–623,654. (In Chinese)
[31] Ni-jia-ti M, Ai-hai-ti D, Huo-jia A, Wu-mai-er P, A-bu-li-zi A, Shi Y, *et al*. Development of a risk-stratification scoring system for predicting lymphovascular invasion in breast cancer. BMC Cancer. 2020; 20: 94.
[32] Zhu HY, Chen JM, Ge YQ, Shao Y, Gao J, Li Y. Preoperative prediction of lymphovascular invasion in invasive breast cancer with MRI radiomics. Chinese Journal of Medical Imaging. 2020; 28: 825–830. (In Chinese)
[33] Pan ZJ, Chen WB. Research progress of magnetic resonance imaging predict lymphovascular invasion in breast cancer. China Medical and Pharmacy. 2022; 12: 65–68,83. (In Chinese)

How to cite this article: Yu-zhou Lai, Chao Tian, Nan-xi Li. Thyroid function and structure variations in female breast cancer patients with diverse pathological characteristics: a retrospective single-center investigation. European Journal of Gynaecological Oncology. 2025; 46(3): 62-73. doi: 10.22514/ejgo.2025.037.