Original Article

High Incidence and Prevalence of Papillary Thyroid Cancer in Breast Cancer Patients

Jung Ho Park , Sanghwa Kim , Lee Su Kim

Division of Breast and Endocrine Surgery, Hallym University Sacred Heart Hospital, Anyang, Korea

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Correspondence to

Lee Su Kim

Division of Breast and Endocrine Surgery,
Hallym University Sacred Heart Hospital, 22,
Gwanpyeong-ro 170-beon-gil, Dongan-gu,
Anyang 14068, Korea.
E-mail: lskim0503@hallym.or.kr

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ORCID iDs

Jung Ho Park
<https://orcid.org/0000-0001-7545-024X>
Sanghwa Kim
<https://orcid.org/0000-0002-1010-3201>
Lee Su Kim
<https://orcid.org/0000-0002-9965-0032>

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Lee Su Kim; Data Curation:
Jung Ho Park, Sanghwa Kim; Investigation:
Jung Ho Park; Supervision: Lee Su Kim;
Validation: Sanghwa Kim; Writing - original
draft: Jung Ho Park; Writing - review & editing:
Sanghwa Kim, Lee Su Kim.

ABSTRACT

Purpose: Breast and thyroid cancers are the two most commonly diagnosed cancers in women. Many studies have described an increased risk of thyroid cancer in breast cancer patients. This may be related to hormonal exposure, genetic susceptibility, detection bias, and cancer treatment. We thus performed a retrospective descriptive study which aimed to assess the incidence and prevalence of thyroid cancer in breast cancer patients.

Methods: We reviewed electronic medical records of breast cancer patients who had undergone surgery between January 2013 and December 2017 in a single tertiary hospital. Patients with recurrent breast cancer, distant metastases, or previous history of thyroidectomy were excluded. A total of 966 patients were enrolled.

Results: A total of 37 (3.8%) patients were diagnosed with both breast and thyroid cancers during 46 months of median follow up. There were 28 (75.7%) synchronous cases diagnosed within 1 year, and 9 (24.3%) metachronous cases diagnosed after 1 year. The median age was 49 years (range, 30–65 years); 34 (91.9%) had thyroid microcarcinoma of less than 1 cm. The incidence and prevalence of thyroid cancer were 2.05 (95% confidence interval [CI], 0.93–3.61) times and 1.41 (95% CI, 0.93–1.98) times higher than those of general population, respectively.

Conclusions: The high incidence and prevalence of thyroid cancer among breast cancer patients are mostly attributable to the widespread screening with ultrasonography. Treatment strategies can be individualized with respect to the tumor characteristics, the patient's preference, and surgical resources.

Keywords: Breast neoplasm; Thyroid neoplasm; Ultrasonography

INTRODUCTION

Breast and thyroid cancers are the two most common cancers in Korean women. The annual incidence of thyroid cancer had peaked in 2012, and it has decreased thereafter. However, since 2016, the incidence of breast cancer exceeded that of thyroid cancer. In 2017, the annual incidence of breast cancer and thyroid cancer were 86.9 cases per 100,000 and 78.5 cases per 100,000 respectively (1). There were 334,017 thyroid cancer patients and 216,402 breast cancer patients among women, and almost 1.3% and 0.8% of Korean women had been

diagnosed with thyroid cancer and breast cancer, respectively. The two cancers comprised about half of all the prevalent cancers among Korean women.

Many studies have described an increased risk of thyroid cancer among breast cancer patients (2-6). Thyroid cancer may be detected during the follow-up of breast cancer patients and vice versa. As breast and thyroid cancers often occur in a single patient, the true association of the two cancers is probable. Hormonal exposure, genetic susceptibility, detection bias, and treatment-related factors have been suggested as reasons for this relationship (7). However, none of the previous studies revealed a single definitive cause of the association. Herein, we aimed to evaluate the incidence and prevalence of thyroid cancer in the newly diagnosed breast cancer patients.

MATERIALS AND METHODS

Study populations

We identified patients who had undergone curative surgery for breast cancer in a single tertiary hospital between January 2013 and December 2017. We reviewed the electronic medical records of 1,139 patients. Patients who had undergone thyroid ultrasonography at least once during the follow-up period were included. We excluded patients with recurrent breast cancer (n=50), distant metastasis (n=2), lobular carcinoma in situ (n=11), unavailable thyroid ultrasonography (n=51), or previous history of thyroidectomy (n=50). We collected data on age at diagnosis of breast cancer, histological type, American Joint Committee on Cancer TNM stage, type of treatment, and follow-up duration.

Screening of thyroid glands

Ultrasonographic examinations of the neck region, including thyroid glands, were performed for multiple purposes, namely to evaluate symptomatic neck mass, incidentally detected thyroid nodule(s) on the chest imaging, and enlarged supraclavicular lymph nodes. All the ultrasonographic examinations were performed and interpreted by radiologists specializing in the breast and thyroid glands. Thyroid nodules with suspicious features were evaluated using a fine-needle aspiration biopsy. In the absence of abnormal findings, follow-up ultrasonography was scheduled after 2 years. Depending on the radiologic and cytologic findings, a thyroidectomy was performed for diagnostic or curative purposes. Before curative surgery, computed tomography for the chest and neck was performed to exclude distant metastases.

Incidence and prevalence of thyroid cancer

Synchronous cases were defined as breast cancer patients who developed thyroid cancer concurrently or within 1 year of follow-up. Metachronous cases were defined as patients who developed thyroid cancer at least 1 year after the diagnosis of primary breast cancer. The incidence of thyroid cancer was calculated as the number of metachronous cases divided by the sum of the time interval between the operation date of the primary breast cancer and the last date of follow up. The standardized incidence of thyroid cancer was estimated using the National Cancer Database in 2017 (1). The standardized incidence ratio was calculated as the observed incidence of thyroid cancer divided by the estimated incidence of thyroid cancer in general population. The prevalence of thyroid cancer was calculated as the number of synchronous thyroid cancer divided by the number of study patients; standardization was done in the same manner.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 24.0, IBM Corp., Armonk, NY, USA). To compare the baseline characteristics of breast cancer patients with or without thyroid cancer, Student's t-test was used. A P value less than 0.05 was considered to be statistically significant. To find risk factors for the development of thyroid cancer, logistic regression analysis was used.

This study was reviewed and approved by the Institutional Review Board (IRB) of Hallym University Sacred Heart Hospital (IRB number, 2020-08-001). The need for informed consent was waived due to the retrospective study design.

RESULTS

A total of 966 patients were included; all of them were female. Among them, 37 (3.8%) patients were diagnosed with both breast and thyroid cancers (**Fig. 1**); 28 (75.7%) were synchronous cases, who were diagnosed with thyroid cancer within 1 year of breast cancer diagnosis; 9 (24.3%) were metachronous cases, who subsequently developed thyroid cancer after 1 year of follow-up.

Clinicopathological characteristics of the breast cancer patients

The baseline characteristics of the breast cancer patients are shown in **Table 1**. The median age was 50 years (range, 24–89 years). Most of the patients had early breast cancer; 862 (89.2%) were stage II or less, 672 (72.5%) underwent chemotherapy, and 823 (85.2%) underwent radiation therapy. The median follow-up period was 46 months. There was no difference in the clinical characteristics between patients with breast cancer only and those with both breast and thyroid cancer. The logistic regression analysis for the prediction of thyroid cancer did not show any clinical factors that were statistically significant.

Fig. 1. Flow-diagram of study design.

Table 1. Clinicopathological characteristics of study patients

Characteristics	Breast cancer only (n=929)	Both breast and thyroid cancer (n=37)	P value
Median age (range) (yr)	50 (24–89)	49 (30–71)	0.36
Operation			0.88
Breast conserving surgery	689 (74.2%)	27 (73.0%)	
Total mastectomy	240 (25.8%)	10 (27.0%)	
Breast cancer stage*			0.68
DCIS†	139 (15.0%)	7 (18.9%)	
I	360 (38.8%)	9 (24.3%)	
II	330 (35.5%)	17 (45.9%)	
III	100 (10.8%)	4 (10.8%)	
Chemotherapy			0.93
No	283 (30.5%)	11 (29.7%)	
Yes	646 (69.5%)	26 (70.3%)	
Radiation treatment			0.44
No	139 (15.0%)	4 (10.8%)	
Yes	790 (85.0%)	33 (89.2%)	
Hormonal treatment			0.39
No	202 (21.7%)	6 (16.2%)	
Yes	727 (78.3%)	31 (83.8%)	

*Anatomical stage according to American Joint Committee on Cancer 7th edition; †Ductal carcinoma in situ.

Clinicopathological characteristics of the thyroid cancer patients

The clinicopathological characteristics of the 37 patients with thyroid cancer are summarized in **Table 2**. All the 37 patients had papillary thyroid cancer; 34 (91.9%) had microcarcinoma

Table 2. Pathological characteristics of thyroid cancers

Characteristics	Number (n=37)
Tumor size	
≤1 cm	34 (91.9%)
>1 cm	3 (8.1%)
Operation	
Hemithyroidectomy	12 (32.4%)
Total thyroidectomy	23 (62.2%)
Total thyroidectomy with unilateral MRND	2 (5.4%)
Lymph node metastasis	
No	25 (67.6%)
Central compartment only	10 (27.0%)
Lateral compartment only	1 (2.7%)
Central & lateral compartment	1 (2.7%)
Extrathyroidal extension	
No	23 (62.2%)
Yes	14 (37.8%)
Lymphovascular invasion	
No	35 (94.6%)
Yes	2 (5.4%)
Thyroiditis	
No	30 (81.1%)
Yes	7 (18.9%)
BRAF V600E mutation	
Not performed	12 (32.4%)
No	3 (8.1%)
Yes	22 (59.5%)
Multiplicity	
Single	28 (75.7%)
Multiple/unilateral	5 (13.5%)
Multiple/bilateral	4 (10.8%)

MRND = Modified radical neck dissection.

Fig. 2. The time interval between the diagnosis of breast cancer and thyroid cancer.

less than 1 cm. Two patients with lateral lymph node metastases underwent lateral neck dissection. Although the tumor size of metachronous cases was smaller than that of synchronous cases, there was no difference regarding cervical lymph node metastases (**Supplementary Table 1**). The time interval between the operation date of breast cancer and thyroid cancer is described in **Fig. 2**. Between 2017 and 2018, the trend in surgery has changed from total thyroidectomy toward hemithyroidectomy (**Fig. 3**).

Incidence and prevalence of thyroid cancer

Of the 966 patients, the number of synchronous thyroid cancer cases was 28 (2.9%). When it was standardized by age and sex, the prevalence of thyroid cancer among our patients was expected to be 19.9 cases (**Supplementary Table 2**). The ratio of standardized prevalence was 1.41 (95% confidence interval [CI], 0.93–1.98).

The observed incidence of metachronous thyroid cancer was 9 patients over 3,731 person-years. When it was standardized, the estimated incidence of thyroid cancer population was 4.39 patients for that 3,731 person-year period (**Supplementary Table 3**). The standardized incidence ratio was 2.05 (95% CI, 0.93–3.61).

Although our observation reveals high incidence and prevalence of thyroid cancer among breast cancer patients, their statistical significance was only marginal.

Fig. 3. The trend regarding the extent of thyroidectomy.

DISCUSSION

The association between breast cancer and thyroid cancer has been suggested in many studies (6-10). In a meta-analysis including 37 studies, there was a 1.55-fold increased risk of thyroid cancer among breast cancer patients (7). Sequelae of a cancer treatment, a shared genetic susceptibility, and hormonal factors have been proposed as the causes of this association. We also demonstrated the high incidence and prevalence of thyroid cancer among newly diagnosed breast cancer patients. A total of 37 (3.8%) patients were diagnosed with both breast and thyroid cancers during the 46-months of median follow-up period. The incidence and prevalence of synchronous thyroid cancer were 2.05 times and 1.41 times higher than those of general population, respectively. However, we could not find any clinicopathological factor that could predict the diagnosis of thyroid cancer.

The exact cause of the association between breast and thyroid cancer has not been well elucidated. Conversely, it was clear that most thyroid cancer diagnoses were attributable to widespread screening with high-resolution ultrasonography. Most of the thyroid cancers were papillary microcarcinomas, detectable on ultrasonography alone. In the previous studies where ultrasonography was used as a screening modality, the prevalence of thyroid cancer was also high (11,12). The incidence of thyroid cancer has increased worldwide as high-resolution ultrasonography has become readily available (13). In particular, thyroid ultrasonography is easily accessible to breast cancer patients. Scanning the breast and thyroid glands can be performed with the same 10 MHz linear probe, and little extra time is needed for the additional thyroid examination (11,12). Due to the easy accessibility, up to 90% of breast cancer patients in our study had undergone thyroid ultrasonography.

Although early screening and diagnosis of thyroid cancer with ultrasonography is generally not recommended, it is useful in some aspects. Specifically, breast cancer and thyroid cancer can be treated at the same time. Simultaneous operation on the two cancers can avoid additional general anesthesia, prevent scheduling conflicts, and reduce net medical expenses. In addition, early diagnosis of thyroid cancer can reduce the extent of surgery. Hemithyroidectomy results in less surgical complications than total thyroidectomy. A large tumor is associated with extrathyroidal extension and cervical lymph node metastases; thus it is more likely to require total thyroidectomy (14,15).

The high detection rate of thyroid cancer by ultrasonography met with the criticism of overdiagnosis (13). As an alternative to thyroidectomy, active surveillance can be utilized (16-19). The 2015 American Thyroid Association guideline recommended active surveillance in the patients with co-morbidities and patients with a short life expectancy, including patients with malignancies other than thyroid cancer (20). Surgical resection can be safely omitted in the low-risk thyroid cancers, avoiding the issue of overtreatment. While some of low-risk thyroid cancer patients may benefit from active surveillance, it may be not suitable for others (**Fig. 4**). Although a substantial number of the patients experienced progression of thyroid cancer during the active surveillance trials, there was no reliable clinicopathological factor or molecular marker that can predict the growth of low-risk thyroid cancer (17,19,21). For this reason, a thyroidectomy is still the gold standard treatment in the management of thyroid cancer.

Our study has several limitations. First, it is based on a retrospective review of electronic medical records in a single center. There are various guidelines that have adopted different criteria for the diagnosis and management of thyroid nodules (20,22). We cannot generalize

Fig. 4. Ultrasonographic features of histologically confirmed papillary thyroid carcinoma. (A) A 60-year-old female patient. A 0.2 cm hypoechoic thyroid nodule was detected in the left middle lobe. It had grown to 0.5 cm over 42 months. (B) A 59-year-old female patient. A 0.5 cm hypoechoic nodule was detected in the right middle lobe. The nodule did not change during the 38 months of follow-up. The tumor abutting the posterior capsule was not suitable for observation.

these results in other institutions with different policies. Second, the small sample size and short duration of follow-up limited our observations. The observed incidence and prevalence of thyroid cancer did not reach the desirable statistical significance. We did not observe any recurrence of thyroid cancer in our study. Third, our study did not include the patients who developed breast cancer following the diagnosis of thyroid cancer. Additionally, because we already excluded the patients who had undergone thyroidectomy, the prevalence of thyroid cancer may be underrated.

In summary, we observed a high incidence and prevalence of thyroid cancer among breast cancer patients. This is mostly attributable to easy access to high-resolution ultrasonography. As the problem of overdiagnosis has been highlighted, an active surveillance approach should be considered in selected cases. Management of the thyroid cancer should be individualized considering the treatment schedule, life expectancy, patient's preferences, and available surgical resources.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Comparison of tumor characteristics between synchronous and metachronous cases

[Click here to view](#)

Supplementary Table 2

Expected prevalence of synchronous thyroid cancer standardized by age and sex

[Click here to view](#)

Supplementary Table 3

Expected incidence of metachronous thyroid cancer standardized by age and sex

[Click here to view](#)

REFERENCES

1. Korea Central Cancer Registry, National Cancer Center. Annual Report of Cancer Statistics in Korea in 2017. Sejong: Ministry of Health and Welfare; 2019.
2. Jung SH, Kwak SS, Kim SC, Park MK, Lee GS, Kim HJ, et al. Clinical characteristics of multiple primary cancer in breast cancer patients. *J Breast Cancer* 2007;10:263-8.
[CROSSREF](#)
3. Kim BK, Oh SJ, Song JY, Lee HB, Park MH, Jung Y, et al. Clinical characteristics and prognosis associated with multiple primary cancers in breast cancer patients. *J Breast Cancer* 2018;21:62-9.
[PUBMED](#) | [CROSSREF](#)
4. Kim JY, Song HS. Metachronous double primary cancer after treatment of breast cancer. *Cancer Res Treat* 2015;47:64-71.
[PUBMED](#) | [CROSSREF](#)
5. Lee J, Park S, Kim S, Kim J, Ryu J, Park HS, et al. Characteristics and survival of breast cancer patients with multiple synchronous or metachronous primary cancers. *Yonsei Med J* 2015;56:1213-20.
[PUBMED](#) | [CROSSREF](#)
6. Zhang L, Wu Y, Liu F, Fu L, Tong Z. Characteristics and survival of patients with metachronous or synchronous double primary malignancies: breast and thyroid cancer. *Oncotarget* 2016;7:52450-9.
[PUBMED](#) | [CROSSREF](#)
7. Nielsen SM, White MG, Hong S, Aschebrook-Kilfoy B, Kaplan EL, Angelos P, et al. The breast-thyroid cancer link: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2016;25:231-8.
[PUBMED](#) | [CROSSREF](#)
8. Park JS, Oh KK, Kim EK, Chang HS, Hong SW. Sonographic screening for thyroid cancer in females undergoing breast sonography. *AJR Am J Roentgenol* 2006;186:1025-8.
[PUBMED](#) | [CROSSREF](#)
9. Lee HK, Hur MH, Ahn SM. Diagnosis of occult thyroid carcinoma by ultrasonography. *Yonsei Med J* 2003;44:1040-4.
[PUBMED](#) | [CROSSREF](#)
10. An JH, Hwangbo Y, Ahn HY, Keam B, Lee KE, Han W, et al. A possible association between thyroid cancer and breast cancer. *Thyroid* 2015;25:1330-8.
[PUBMED](#) | [CROSSREF](#)
11. Lei K, He X, Yu L, Ni C, Chen H, Guan D, et al. Breast cancer prognosis is better in patients who develop subsequent metachronous thyroid cancer. *PLoS One* 2019;14:e0215948.
[PUBMED](#) | [CROSSREF](#)
12. Kim JH, Kang I, Nam S, Park HS, Park S, Jeong JJ, et al. Comparison of characteristics in patients with both thyroid and breast cancer: based on order of incidence. *Korean J Clin Oncol* 2017;13:1-9.
[CROSSREF](#)
13. Roman BR, Morris LG, Davies L. The thyroid cancer epidemic, 2017 perspective. *Curr Opin Endocrinol Diabetes Obes* 2017;24:332-6.
[PUBMED](#) | [CROSSREF](#)
14. Youngwirth LM, Adam MA, Scheri RP, Roman SA, Sosa JA. Extrathyroidal extension is associated with compromised survival in patients with thyroid cancer. *Thyroid* 2017;27:626-31.
[PUBMED](#) | [CROSSREF](#)
15. Kim SK, Park I, Woo JW, Lee JH, Choe JH, Kim JH, et al. Predictive factors for lymph node metastasis in papillary thyroid microcarcinoma. *Ann Surg Oncol* 2016;23:2866-73.
[PUBMED](#) | [CROSSREF](#)

16. Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. *World J Surg* 2016;40:516-22.
[PUBMED](#) | [CROSSREF](#)
17. Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, et al. Active surveillance for patients with papillary thyroid microcarcinoma: a single center's experience in Korea. *J Clin Endocrinol Metab* 2017;102:1917-25.
[PUBMED](#) | [CROSSREF](#)
18. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg* 2017;143:1015-20.
[PUBMED](#) | [CROSSREF](#)
19. Oh HS, Ha J, Kim HI, Kim TH, Kim WG, Lim DJ, et al. Active surveillance of low-risk papillary thyroid microcarcinoma: a multi-center cohort study in Korea. *Thyroid* 2018;28:1587-94.
[PUBMED](#) | [CROSSREF](#)
20. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1-133.
[PUBMED](#) | [CROSSREF](#)
21. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid* 2016;26:144-9.
[PUBMED](#) | [CROSSREF](#)
22. Park JW, Chung KW, Yun JS, Kwon H, Kim HY, Nam KH, et al. Surgical treatment guidelines for patients with differentiated thyroid cancer: the Korean Association of Thyroid and Endocrine Surgeons (KATES). *Korean J Endocr Surg* 2017;17:1-18.
[CROSSREF](#)