
Risk of Breast Cancer in Patients with Thyroid Cancer Receiving or Not Receiving ¹³¹I Treatment: A Nationwide Population-Based Cohort Study

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An increased risk of second primary malignancy after ¹³¹I therapy has been reported. The objective of this study was to determine the risk of breast cancer in patients with thyroid cancer receiving or not receiving radioiodine treatment in Taiwan. **Methods:** This nationwide population-based cohort study was conducted using data obtained from the Taiwan National Health Insurance Database from 2000 to 2011. A total of 10,361 female patients with thyroid cancer (3,292 did not receive ¹³¹I treatment and 7,069 received ¹³¹I treatment) were enrolled, and 41,444 female controls were frequency-matched to the thyroid cancer patients in a 1:4 ratio by age (5-y age group). A Cox proportional hazards model was applied to estimate the risk of breast cancer in thyroid cancer patients receiving or not receiving ¹³¹I treatment in terms of hazard ratios and 95% and 98% confidence intervals. **Results:** The incidence rates of breast cancer in patients with thyroid cancer receiving ¹³¹I therapy, those not receiving ¹³¹I therapy, and controls were 18.9, 17.7, and 13.1 per 10,000 person-years, respectively. Compared with patients with thyroid cancer treated with a cumulative ¹³¹I dose of 4.44 GBq or less, the risk of breast cancer was not significantly increased in those treated with a cumulative ¹³¹I dose of more than 4.44 GBq (adjusted hazard ratio, 0.78; 95% confidence interval, 0.50–1.21, *P* = 0.26; 98% confidence interval, 0.45–1.33, *P* > 0.02). **Conclusion:** The greatest increased risk of breast cancer in patients with thyroid cancer is associated with the fact that the patient has thyroid cancer regardless of ¹³¹I administration. However, ¹³¹I further increased that risk but not as much as just having thyroid cancer.

Key Words: ¹³¹I therapy; breast cancer; thyroid cancer; Taiwan National Health Insurance Database

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The incidence of thyroid cancer is increasing worldwide (1–3). The Taiwan Cancer Registry Annual Report 2012 published by the Bureau of Health Promotion, Department of Health, revealed that thyroid cancer is the fifth leading cause of death in women. The most common histologic subtype of thyroid cancer is papillary carcinoma, followed by follicular carcinoma. The definitive therapy for differentiated thyroid cancer is surgical thyroidectomy, with or without adjuvant radioiodine therapy, depending on histologic information and the presence of residual, unresectable, and metastatic disease (4–7). Chemotherapy or radiotherapy may also be used in cases of distant metastases or an advanced cancer stage (8). The 5-y survival rate of all people with thyroid cancer is approximately 98% (9,10).

The sodium-iodide symporter (NIS) is extremely relevant clinically, because it enables the treatment of thyroid cancer patients with radioiodine (11–13). The NIS is also found in the breasts, salivary lacrimal glands, gastric mucosa, and ovaries (14,15). However, concerns have been raised regarding radioactive iodine therapy, because of the potential for the development of second primary malignancy, including breast cancer (16). In Taiwan, the malignancy with the highest incidence in women was breast cancer in 2012 (17). Because of a long life expectancy in most thyroid cancer survivors, it is crucial to comprehensively evaluate the risk of breast cancer in patients with thyroid cancer receiving or not receiving ¹³¹I therapy. Hence, we conducted a nationwide cohort study of patients with thyroid cancer identified from the Taiwan National Health Insurance Database (NHIRD) to investigate the risk of breast cancer in patients with thyroid cancer receiving or not receiving ¹³¹I therapy.

MATERIALS AND METHODS

Data Source

The National Health Insurance (NHI) program was established in Taiwan in 1995 to provide comprehensive health care to the nation's residents. The NHI program covers approximately 99% of the Taiwanese population (~23.75 million) (18). The National Health Research Institutes (NHRI) is responsible for managing NHI claims data. It has established the NHIRD and releases this database annually to the public for research purposes. The NHRI encrypts all information that may potentially identify any individual patient. For this study, we used a subset of the NHIRD that contains health care data including files in the Registry

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for Catastrophic Illness Patient Database, Longitudinal Health Insurance Database 2000 (LHID 2000), and registry for beneficiaries. Disease diagnoses are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the institutional review board of China Medical University (CMUH-104-REC2-115). The institutional review board also specifically waived the consent requirement.

Sampled Patients

From the Registry for Catastrophic Illness Patient Database, we identified female patients aged older than 20 y who were newly diagnosed with thyroid cancer (ICD-9-CM code 193) from 2000 to 2008. These patients comprised the thyroid cancer cohort, which was divided into 2 groups on the basis of ^{131}I therapy status. The index date for each patient receiving ^{131}I therapy was the first date on which ^{131}I therapy was received. The index date for patients not receiving ^{131}I therapy was the date of randomly assigned month and day with the same index year of the patient receiving ^{131}I therapy. Finally, we extracted data on 10,361 female patients with thyroid cancer without any other cancer history (ICD-9-CM codes 140–208) before the index date. Among them, 7,069 female patients received ^{131}I therapy and 3,292 did not. Controls (without thyroid cancer or any other cancer at baseline) were identified from the LHID 2000. For each thyroid cancer patient, 4 controls were randomly selected from the pool of participants without thyroid cancer and any other cancer at the baseline, frequency-matched by the year of index date and age (every 5-y span).

Outcome

All study patients were observed until they were diagnosed with breast cancer, lost to follow-up, died, or withdrew from the NHI program, or until December 31, 2011.

Variables of Interest

Information extracted from the claims data included age and the Charlson comorbidity index (CCI) score. We categorized the CCI score into 4 levels: 0, 1, 2, and 3 or more. The CCI score was calculated for each patient according to the claims data for hospitalization at the baseline. The CCI score is a scoring system that includes weighting factors on crucial concomitant diseases and has been validated for use with ICD-9-CM-coded administrative databases (19,20). The adjusted factors included obesity (ICD-9-CM code 278), alcohol-related illness (ICD-9-CM code 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), diabetes (ICD-9-CM code 250), lung metastases (ICD-9-CM code 197), benign neoplasm of breast (ICD-9-CM code 217), hormone therapy, mammography, and ultrasonography. We also considered thyroid cancer-related treatments including radiotherapy, chemotherapy, and thyroxine.

Statistical Analysis

A χ^2 test and Student *t* test were used to evaluate differences in categorical and continuous variables, respectively, between the thyroid cancer and comparison cohorts. The incidence of breast cancer in the 3 cohorts was calculated during the follow-up period. Univariate and multivariate Cox proportional hazards regression analyses used to estimate the association between the risk of breast cancer and the ^{131}I therapy status hazard ratios are presented with 95% and 98% confidence intervals using the Cox models. The Bonferroni adjustment was used in multiple comparisons. Further analysis was performed to assess the effect of the ^{131}I dose on the risk of breast cancer according to the cumulative ^{131}I dose (in GBq) for patients receiving ^{131}I during the study period. All data analyses were performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc.). Two-tailed *P* values of less than 0.05 and 0.02 were considered significant.

RESULTS

Table 1 presents the baseline demographic factors, comorbidities, medication, imaging examinations, and treatments of patients in the 3 cohorts. Most patients in the 3 cohorts were aged 49 y or younger. Significant differences were observed in the number of patients with a CCI score of 1 or greater among the 3 cohorts ($P < 0.001$). The proportions of patients with a CCI score of 1 or greater were 11.45% in the thyroid cancer without ^{131}I therapy cohort, 7.86% in the thyroid cancer with ^{131}I therapy cohort, and 6.76% in the comparison cohort. In thyroid cancer patients, the proportions of those with obesity, diabetes, lung metastases, or benign neoplasm of the breast; those who had received hormone therapy; and those who had undergone mammography and ultrasound were significantly higher than the comparison cohort (all $P < 0.001$). Compared with the patients with thyroid cancer receiving ^{131}I treatment, a significantly higher proportion of the patients with thyroid cancer not receiving ^{131}I treatment underwent radiotherapy and chemotherapy ($P < 0.001$). A significantly higher proportion of the patients with thyroid cancer receiving ^{131}I treatment took a thyroxine supplement. The overall incidence of breast cancer was higher in the thyroid cancer cohort than in the comparison cohort (18.6 vs. 13.1 per 10,000 person-years). The median follow-up time of the comparison cohort was 6.58 y (interquartile range, 4.40–9.12) and of the thyroid cancer cohort 6.51 y (interquartile range, 4.34–9.11). Compared with the comparison cohort, the risk of breast cancer was significantly higher in the thyroid cancer cohort (adjusted HR [aHR], 1.31; 95% confidence interval [CI], 1.07–1.61; 98% CI, 1.02–1.68). The risk of breast cancer was significantly higher in the patients with thyroid cancer treated with ^{131}I than in the controls (aHR, 1.34; 95% CI, 1.15–1.69; 98% CI, 1.01–1.78) (Table 2).

After stratification by age, in patients older than 65 y, the patients with thyroid cancer not receiving ^{131}I treatment had a significantly higher risk of breast cancer than that of the controls (aHR, 2.83; 95% CI, 1.15–6.93); however, the risk became not significant with Bonferroni adjustment (aHR, 2.82; 98% CI, 0.95–8.40) (Table 3). We compared the risk of breast cancer according to follow-up period. For a follow-up period of longer than 5 y, the patients with thyroid cancer receiving ^{131}I treatment had a significantly higher risk of breast cancer than that of the controls (aHR, 1.81; 95% CI, 1.27–2.57; 98% CI, 1.18–2.77) (Table 4). Compared with patients with thyroid cancer treated with a cumulative ^{131}I dose of 4.44 GBq or less, those treated with a cumulative ^{131}I dose greater than 4.44 GBq did not have a significantly increased risk of breast cancer (aHR, 0.78; 95% CI, 0.45–1.33; 98% CI, 0.45–1.33) (Table 5).

DISCUSSION

Thyroid cancer is the most common endocrine malignancy. It was estimated that more than 60,000 new cases of thyroid cancer would be diagnosed in the United States in 2014 and that almost 1,900 patients would die from this disease (21,22). Multiple primary tumors account for 13.1% of cancers in men and 13.7% of cancers in women, and all cancer survivors have a 2-fold-greater probability of developing a second primary cancer than cancer-free people. The co-occurrence of multiple malignancies could be random or associated with risk factors such as an environmental or genetic predisposition and therapy-related effects (16,23,24). Thyroid remnants ablation is not necessary in patients with low-risk thyroid cancer. An increased risk of second primary malignancy after ^{131}I therapy has been reported. A previous study found that the incidence of second primary malignancy may be radically increased in patients who have received

TABLE 1
Demographic Factors, Comorbidities, Medication, and Imaging Examinations of Study Participants According to Thyroid Cancer Status

Variable	Control (n = 41,444)		Thyroid cancer						P
	n	%	All (n = 10,361)		Without ¹³¹ I treatment (n = 3,292)		With ¹³¹ I treatment (n = 7,069)		
			n	%	n	%	n	%	
Age (y)									0.99
≤49	26,184	63.2	6,546	63.2	1,996	60.6	4,550	64.4	
50–64	10,740	25.9	2,685	25.9	861	26.2	1,824	25.8	
>65	4,520	10.9	1,130	10.9	435	13.2	695	9.83	
Mean (SD)	46.0	14.3	46.2	13.9	47.2	14.7	45.7	13.5	0.17
CCI score									<0.001*
0	38,642	93.2	9,429	91.0	2,915	88.6	6,514	92.2	
1	1,812	4.37	630	6.08	235	7.14	395	5.59	
2	514	1.24	183	1.77	80	2.43	103	1.46	
3+	476	1.15	119	1.15	62	1.88	57	0.81	
Obesity	643	1.55	283	2.73	78	2.37	205	2.90	<0.001
Alcohol-related illness	519	1.25	113	1.09	42	1.28	71	1.00	0.18
Diabetes	2,405	5.80	820	7.91	269	8.17	551	7.79	<0.001
Lung metastases	8	0.02	95	0.92	17	0.52	78	1.10	<0.001
Benign neoplasm of the breast	1,173	2.83	599	5.78	171	5.19	428	6.05	<0.001
Hormone therapy	12,443	30.0	3,627	35.0	1,074	32.6	2,553	36.1	<0.001
Mammography	3,412	8.23	1,406	13.6	409	12.4	997	14.1	<0.001
Ultrasonography	1,498	3.61	781	7.54	237	7.20	544	7.70	<0.001
Treatment									
Radiotherapy			479	4.62	179	5.44	300	4.24	<0.001†
Chemotherapy			240	2.32	112	3.40	128	1.81	<0.001†
Thyroxine			6,960	67.2	1,771	53.8	5,189	73.4	<0.001†

*Comparison between breast cancer and control.

†Comparison between thyroid cancer without ¹³¹I treatment and thyroid cancer with ¹³¹I treatment.

an extremely high cumulative activity (>40 GBq) of ¹³¹I (25). Lang et al. reported that the occurrence of second primary malignancy adversely affected the survival of differentiated thyroid

cancer (26). Hsu et al. reported that the incidence rate of co-occurring breast cancer and thyroid cancer in women was 1.59%, and the strength of the association was intermediate (16).

TABLE 2
Crude and Adjusted HRs for Breast Cancer Among Thyroid Cancer and Control Groups

Analyzed results	Control	Thyroid cancer	Thyroid cancer without ¹³¹ I treatment	Thyroid cancer with ¹³¹ I treatment
No. of breast cancer	368	129	38	91
Person-years	280,940	69,554	21,439	48,115
Incidence rates	13.1	18.6	17.7	18.9
Crude HR (95% CI)	1.00	1.41 (1.16–1.73)	1.35 (0.97–1.89)	1.44 (1.15–1.81)
Adjusted HR (95% CI)	1.00	1.31 (1.07–1.61)	1.26 (0.90–1.76)	1.34 (1.06–1.69)
Crude HR (98% CI)	1.00	1.41 (1.11–1.81)	1.35 (0.90–2.03)	1.44 (1.09–1.91)
Adjusted HR (98% CI)	1.00	1.31 (1.02–1.68)	1.26 (0.84–1.89)	1.34 (1.01–1.78)

Adjusted for age, all comorbidities, hormone therapy, mammography, and ultrasonography.

TABLE 3
Adjusted HRs for Breast Cancer According to Thyroid Cancer Status Stratified by Age

Age	Control, adjusted HR	Thyroid cancer, adjusted HR	Thyroid cancer	
			Without ¹³¹ I treatment, adjusted HR	With ¹³¹ I treatment, adjusted HR
95% CI				
≤49	1.00	1.18 (0.89–1.55)	0.94 (0.57–1.57)	1.27 (0.94–1.73)
50–64	1.00	1.36 (0.98–1.90)	1.43 (0.85–2.40)	1.33 (0.91–1.96)
>65	1.00	1.74 (0.86–3.52)	2.83 (1.15–6.93)	1.18 (0.45–3.09)
98% CI				
≤49	1.00	1.17 (0.84–1.64)	0.94 (0.51–1.75)	1.27 (0.87–1.84)
50–64	1.00	1.38 (0.93–2.06)	1.43 (0.76–2.70)	1.36 (0.85–2.16)
>65	1.00	1.69 (0.71–3.98)	2.82 (0.95–8.40)	1.14 (0.35–3.66)

Adjusted for all comorbidities, hormone therapy, mammography, and ultrasonography.

In our study, patients with thyroid cancer treated with ¹³¹I had a significantly increased risk of breast cancer compared with controls. After patients with a follow-up duration of less than 3 y were excluded, the results were still the same (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>) (25). Physicians may propose that patients with thyroid cancer perform breast self-examinations periodically and undergo ultrasonographic mammography regularly. It has been reported that there is an association between breast cancer and thyroid cancer; this association may be attributable to common etiologic features, pathologic processes, or treatment-related factors (27,28) that these 2 cancers share. Previous studies suggested the relationship between serum levels of thyroid hormones or thyroid peroxidase autoantibodies and the risk or prognosis of breast cancer (29–32). Radioiodine therapy is the main postoperative treatment for patients with differentiated thyroid cancer. The presence of the NIS in thyroid cancer cells enables highly efficient iodine accumulation, which facilitates the use of radioactive substrates for therapeutic purposes (33). Stimulating NIS expression by elevating thyroid-stimulating hormone levels is therefore required before ¹³¹I administration (34,35). Studies have reported that enhanced NIS expression caused by hyperprolactinemia or individual vari-

ations might be a mechanism of radioiodine uptake in nonlactating breasts (36,37). The seminal study in which NIS expression in lactating breasts was discovered showed that this protein was expressed in more than 80% of both invasive and in situ breast cancers (33,38). The stimulation of NIS expression in patients with thyroid cancer before ¹³¹I therapy may motivate NIS expression in the breast, resulting in an increased risk of breast cancer. Previous reports have indicated that women and men with thyroid cancer have a risk of breast cancer (33).

We found that the risk of breast cancer was significantly higher in young (≤49 y) patients with thyroid cancer treated with ¹³¹I; this increased risk may be attributable to the stimulation of NIS expression before ¹³¹I therapy and the long latency of radiogenic malignancy. In the past decade, thyroid cancer was found to be the leading malignancy incidentally detected using ¹⁸F-FDG PET during health checkups or for staging or restaging patients with cancer. Another possible reason for detecting breast cancer in young patients with thyroid cancer is aggressive examination after the primary cancer was found (39,40).

Rubino et al. found a correlation between the ¹³¹I dose and number of second primary malignancies per number of person-years of follow-up. They concluded that the risk of solid tumors

TABLE 4
Adjusted HRs for Breast Cancer According to Thyroid Cancer Status Stratified by Follow-up Time

Follow-up time (y)	Control, adjusted HR	Thyroid cancer, adjusted HR	Thyroid cancer	
			Without ¹³¹ I treatment, adjusted HR	With ¹³¹ I treatment, adjusted HR
95% CI				
≤5	1.00	1.14 (0.87–1.48)	1.25 (0.82–1.88)	1.09 (0.80–1.49)
>5	1.00	1.65 (1.20–2.26)	1.28 (0.72–2.26)	1.81 (1.27–2.57)
98% CI				
≤5	1.00	1.14 (0.82–1.57)	1.25 (0.75–2.06)	1.09 (0.75–1.59)
>5	1.00	1.65 (1.12–2.42)	1.28 (0.64–2.56)	1.81 (1.18–2.77)

Adjusted for age, all comorbidities, hormone therapy, mammography, and ultrasonography.

TABLE 5
Incidence Rates and HRs of Breast Cancer in Thyroid Patients with Different Dose of ¹³¹I Treatment

Variable	n	Event	Person-year	Incidence density rates	Adjusted HR (95% CI)	Adjusted HR (98% CI)	Adjusted HR (95% CI)	Adjusted HR (98% CI)
Without ¹³¹ I treatment	3,292	38	21,439	17.7	1.00	1.00		
With ¹³¹ I treatment, cumulative ¹³¹ I dose (GBq)								
≤4.44	4,221	61	29,117	21.0	1.18 (0.79–1.77)	1.18 (0.72–1.93)	1.00	1.00
>4.44	2,848	30	18,998	15.8	0.90 (0.56–1.46)	0.90 (0.50–1.63)	0.78 (0.50–1.21)	0.78 (0.45–1.33)

Adjusted for age, all comorbidities, hormone therapy, mammography, ultrasonography, radiotherapy, chemotherapy, and thyroxine supplement.

and leukemia is increased in patients with an increased cumulative administered dose of ¹³¹I (41). Lang et al. reported that the cumulative radioiodine therapy activity was the only independent risk factor for second primary cancer in thyroid cancer survivors (42). The risk of second primary malignancies including hematologic cancer, head and neck cancer, cancer in the abdomen except in the genitourinary system, cancer out of the abdomen, uterine cancer, prostate cancer, urinary system cancer, and other cancer type receiving ¹³¹I treatment were compared with those not receiving ¹³¹I treatment in Ko's study (43). Ko et al. reported that ¹³¹I treatment resulted in marginally higher secondary cancer incidence, which was not related to the cumulative ¹³¹I dose (43). We found that the risk of breast cancer was not significantly increased in patients with thyroid cancer treated with a cumulative ¹³¹I dose greater than 4.44 GBq compared with patients treated with a cumulative ¹³¹I dose of 4.44 GBq or less. According to our study findings, we hypothesized that the stimulation of NIS expression before ¹³¹I treatment may have stronger effects on the risk of breast cancer in patients with thyroid cancer than radiation exposure does. Further research is required to confirm our hypothesis.

This study has limitations. First, the NHIRD provides no detailed information on patients regarding factors such as their lifestyle, behavioral habits, body mass index, physical activity, socioeconomic status, and family history, all of which are possible confounding factors in this study. Second, the evidence derived from a retrospective cohort study is typically lower in statistical quality because of many sources of inherent bias and the necessary adjustments for confounding factors. Third, the registries in the NHI claims are primarily used for administrative billing and have not been verified for scientific purposes. Fourth, under the regulations of the Personal Information Protection Act in Taiwan, no individual patient's medical chart and data could be directly checked, because of the anonymity of the identification number for every patient. Therefore, we could not obtain additional information such as the ¹³¹I absorbed dose, ¹³¹I posttherapy scintigraphy or the findings on the radioiodine scan with no uptake in the breast, focal uptake in the breast, or diffuse uptake in the breast by directly contacting the patients. However, the data on diagnoses in the NHIRD are highly reliable. The insurance program has mechanisms for monitoring insurance claims.

CONCLUSION

The greatest increased risk of breast cancer in patients with thyroid cancer is associated with the fact that the patient has thyroid cancer regardless of ¹³¹I administration. However, ¹³¹I further increased that risk but not as much as having thyroid cancer.

DISCLOSURE

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