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Cancer Risk in Patients with Graves' Disease: A Nationwide Cohort Study

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Background: The possibility of an association of Graves' disease (GD) with subsequent cancers has been previously reported.
Methods: Our study used the Taiwanese National Health Insurance Research Database (NHIRD), which identified 5025 newly diagnosed GD patients from 1997 to 2010, and 20,100 frequency matched non-GD patients. The risk of developing cancer for GD patients was measured using the Cox proportional hazard model.
Results: The incidence of developing cancer in the GD cohort was 4.92 per 1000 person-years and was 1.37-fold higher than in the comparison cohort ($p < 0.001$). Compared with patients aged 20–34 years, older age groups demonstrated a higher risk of developing cancer (35–49 years: hazard ratio (HR) = 4.15; 50–64 years: HR = 7.39; ≥ 65 years: HR = 13.4). After adjusting for sex, age, and comorbidities, the HR for developing breast cancer and thyroid cancer was 1.58- and 10.4-fold higher for patients with GD. Furthermore, the incidence rates (IRR) were the highest in the first three years: 2.06 [confidence interval (CI) = 1.87–2.27] and 15.6 [CI = 13.9–17.5] in breast cancer and thyroid cancer with GD respectively. Specifically, a 16-fold hazard of developing thyroid cancer was present in the first three years in the GD cohort compared to the non-GD cohort [CI = 7.95–32.1].
Conclusions: GD patients have a higher risk of cancer, particularly thyroid and breast cancer sequent within six and three years respectively. Strategies for preventing thyroid and breast cancer are proposed.

Introduction

Graves' disease (GD) affects ~0.5% of the population, and is the underlying cause of 50–80% of cases of hyperthyroidism (1,2). GD has the highest risk of onset between the ages of 40 and 60 years; it is the most prevalent autoimmune disorder in the United States (3,4). The prevalence of GD is similar among Caucasians and Asians, but it is lower among African Americans (3).

Certain studies have examined the possibility of an association of GD with subsequent types of cancer. Subsequent types of cancer could be caused by the autoimmunity of GD (5). Cancer may occur because of an abnormal host immune system tolerance (6). Other studies have suggested that a higher incidence of subsequent cancer exists in patients with autoimmune thyroid diseases (7,8).

Hyperthyroidism apparently does not protect patients from thyroid cancer (9). An increased thyroid cancer risk in patients with GD was observed in a population-based cohort study in Sweden (5). Thyroid hormones influence both normal breast cell differentiation and breast cancer cell proliferation, and stimulate the angiogenesis of certain cancer types (10).

The pathogenetic mechanism of interaction between GD and cancer remains unclear. With the increasing incidence of GD, the health consequences of these patients are becoming increasingly important (11,12). The epidemiologic data on the association between GD and cancer provide useful information for primary prevention and etiology research. We conducted a nationwide study to evaluate the cancer risk in Chinese patients with GD.

Methods

Data sources

Data for this study were obtained from the National Health Insurance (NHI) Reimbursement Database, and relied on compulsory widespread health insurance since the inauguration of the NHI in Taiwan in 1995. This database covers nearly all inpatient and outpatient medical claims data,

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including sociodemographic information, details of inpatient and outpatient orders, ambulatory healthcare, prescriptions, and dates of admission and discharge for the 23 million residents of Taiwan (13). The data for each inpatient and outpatient visits contained up to five diagnoses that were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (14). Data files were linked with patient identifications, which had been anonymized and maintained by the NHI reimbursement database as files suitable for public research. Each data set can be interlinked according to a patient's unique personal identification number. The data sets were released with secondary identified data for research; the study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012).

Study patients

In this longitudinal cohort study, we selected all adult patients (≥20 years of age) with at least three claims for ambulatory care and hospitalization visits for GD (ICD-9-CM code 242.0) between January 1, 1997, and December 31, 2010. We conducted a systematic random sampling design to select a comparison cohort from the rest of the insured population not diagnosed with GD or cancer. The frequency was matched by age, sex, and the year of index date. All study participant cases were followed from the first reported date of cancer until December 31, 2010. We analyzed data collected from 20,100 patients for the comparison group and 5025 for the study group using the diagnosis date as the index date.

Outcome definition

We obtained data on patients who were diagnosed with cancer from January 1, 1997, to December 31, 2010, from the NHI catastrophic illness registry files. Any diagnosis of cancer except metastatic cancer (ICD-9-CM codes 140–195 and 200–208) were coded by doctors and officials of the NHI. We excluded patients who had any type of cancer (ICD-9-CM codes 140–208) before the index date. We divided the cancers into the following 14 groups: head and neck cancer (ICD-9-CM codes 140–149), stomach cancer (ICD-9-CM code 151), colon cancer (ICD-9-CM codes 153 and 154), hepatoma (ICD-9-CM code 155), lung cancer (ICD-9-CM code 162), breast cancer (ICD-9-CM code 174), uterine cancer (ICD-9-CM codes 179 and 182), cervical cancer (ICD-9-CM code 180), prostate cancer (ICD-9-CM code 185), bladder cancer (ICD-9-CM code 188), kidney cancer (ICD-9-CM code 189), thyroid cancer (ICD-9-CM code 193), hematologic cancer (ICD-9-CM codes 200–208), and other cancer types.

Variables of exposure

We also assessed patients who had at least three claims for ambulatory care visits or hospitalization visits at the baseline with principal/secondary diagnoses of the following diseases, which were considered possible confounding factors associated with cancer: hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), and hyperlipidemia (ICD-9-CM code 272). These were all recognized from the claims data as baseline comorbidities.

Statistical analysis

The relevant findings were determined as mean ± standard deviation, or frequency (relative frequency, %). The differences among continuous variables were estimated using *t*-tests, and the differences among categorized variables were analyzed using a chi-square test. Person-years for the follow-up period were calculated for each patient until cancer diagnosis or censor. The person-years and overlapping confidence interval (CI) were calculated to assess incidence density rates. To compare the study cohort to the comparison cohort rate, ratios were examined using the Poisson regression model. Moreover, Cox proportional-hazards regression analysis was used to assess the cancer risk associated with toxic diffuse goiters, adjusting for covariates significantly related to toxic diffuse goiters. Statistical significance was accepted at $p = 0.05$. The SAS statistical package (v9.2 for Windows; SAS Institute, Inc., Cary, NC) was used to manage and analyze the data.

Results

More female patients were present in our study, and more than half of them were less than 50 years of age (Table 1). No significant differences in sex and age between the GD and non-GD group were found (mean age 41.7 ± 13.8 years vs. 41.6 ± 13.9 years respectively). GD patients more likely tended to have hypertension, diabetes mellitus, and hyperlipidemia than the comparison group. Between the GD and non-GD cohorts, the incidence density rates of cancer were 4.92 and 3.58 per 1000 person-years respectively (Table 2). The overall incidence rate of cancer was 37% higher in the GD cohort than in the comparison cohort, with an adjusted hazard ratio (aHR) of 1.35 [CI = 1.12–1.62]. Stratified by sex, the incidence density rates were 5.02 and 4.89 per 1000 person-years in men and women with GD, and had a 34% and 38% increased cancer risk compared to non-GD cohorts respectively. Stratified by age, the incidence density rate was highest in patients older than 65 years (12.27 per 1000 person-years). The age-specific rate ratio showed that patients with GD had a higher incidence density rate ratio (IRR) for cancer between the ages of 20 and 34 years compared to the comparison cohort (IRR = 2.60 [CI = 2.24–3.01]). After adjusting for sex, age, and

Table 1. Comparison in Demographic Characteristics and Comorbidities in Patients With and Without Graves' Disease

	Graves' disease [n *(%)*]		
	Without (N = *20,100*)	*With* (N = *5025*)	p *Value*
Sex			
Women	15,540 (77.3)	3885 (77.3)	0.99[a]
Men	4560 (22.7)	1140 (22.7)	
Age-stratified			
20–34	6866 (34.2)	1709 (34.0)	0.99[a]
35–49	7661 (38.1)	1914 (38.1)	
50–64	3970 (19.8)	999 (19.9)	
≥65	1603 (7.98)	403 (8.02)	
Age, mean ± SD	41.6 ± 13.9	41.7 ± 13.8	0.81[b]
Comorbidity			
Diabetes	1353 (6.73)	553 (11.0)	< 0.0001[a]
Hypertension	2867 (14.3)	953 (19.0)	< 0.0001[a]
Hyperlipidemia	1987 (9.89)	670 (13.3)	< 0.0001[a]

Statistical significance determined by [a]chi-square test or [b]*t*-test.
SD, standard deviation.

Table 2. Comparison of Incidence Densities of Cancer and Hazard Ratio Between Patients With and Without Graves' Disease by Demographic Characteristics

	Graves' disease							
	Without			*With*				
	Event	*PY*	*Rate*[a]	*Event*	*PY*	*Rate*[a]	*IRR*[b] *[CI]*	*Adjusted HR*[b] *[CI]*
All cancer	457	127,623	3.58	158	32,140	4.92	1.37 (1.26, 1.49)***	1.35 (1.12, 1.62)**
Sex								
F	352	99,654	3.53	123	25,172	4.89	1.38 (1.26, 1.52)***	1 (Reference)
M	105	27,969	3.75	35	6968	5.02	1.34 (1.12, 1.59)**	0.99 (0.82, 1.19)
Age								
20–34	30	44,891	0.67	20	11,527	1.74	2.60 (2.24, 3.01)***	1 (Reference)
35–49	164	50,044	3.28	67	12,401	5.40	1.65 (1.44, 1.88)***	4.15 (3.06, 5.64)***
50–64	159	24,203	6.57	44	6012	7.32	1.11 (0.92, 1.35)	7.39 (5.38, 10.2)***
≥65	104	8485	12.26	27	2200	12.27	1.00 (0.76, 1.32)	13.4 (9.43, 19.1)***
Diabetes								
No	388	120,323	3.22	128	28,860	4.44	1.38 (1.26, 1.50)***	1 (Reference)
Yes	69	7300	9.45	30	3280	9.15	0.97 (0.74, 1.26)	1.43(1.12, 1.83)**
Hypertension								
No	327	111,504	2.93	120	26,363	4.55	1.55 (1.42, 1.700***	1 (Reference)
Yes	130	16,119	8.07	38	5777	6.58	0.82 (0.66, 1.01)	0.96 (0.77, 1.19)
Hyperlipidemia								
No	380	116,783	3.25	131	28,389	4.61	1.42 (1.30, 1.55)***	1 (Reference)
Yes	77	10,839	7.10	27	3751	7.20	1.01 (0.79, 1.29)	0.93 (0.73, 1.18)

[a]Incidence rate (per 1000 person-years).
[b]Multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, and hyperlipidemia.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
PY, person-years; IRR, Incidence rate ratio (per 1000 person-years); CI, confidence interval; HR, hazard ratio.

comorbidities, the older age groups had a greater hazard ratio (20–34 years of age was used as the reference group). Patients aged 65 years or older showed a 13.4-fold increase [CI = 9.43–19.10]. Analysis for the association of comorbidities showed that patients with diabetes had a higher incidence of cancer, which was slightly lower than in the comparison cohort (9.15 vs. 9.45 per 1000 person-years), and had an aHR of 1.43 [CI = 1.12–1.83]. The analyses of cancer types between GD and non-GD cohorts are shown in Table 3.

Patients with GD had a statistically significant higher incidence density ratio of having head and neck, hepatoma, breast, prostate, and thyroid cancer compared to the

Table 3. Site-Specific Incidence Rate Ratio and Hazard Ratios of Cancer Between Patients With and Without Graves' Disease

	Graves' disease					
	Without		*With*			
Cancer (ICD-9-CM code)	*Event*	*Rate*[a]	*Event*	*Rate*[a]	*IRR [CI]*	*Adjusted HR*[b] *[CI]*
Head and neck (140–149)	22	0.17	8	0.25	1.44 (1.30, 1.61)***	1.28 (0.56, 2.89)
Stomach (151)	21	0.16	5	0.16	0.95 (0.83, 1.07)	0.94 (0.35, 2.51)
Colon (153, 154)	59	0.46	9	0.28	0.61 (0.53, 0.69)***	0.61 (0.30, 1.24)
Hepatoma (155)	42	0.33	13	0.40	1.23 (1.10, 1.37)**	1.13 (0.60, 2.12)
Lung (162)	42	0.33	7	0.22	0.66 (0.58, 0.75)***	0.69 (0.31, 1.54)
Breast (174)	97	0.76	39	1.21	1.60 (1.46, 1.75)***	1.58 (1.09, 2.30)*
Uterus (179, 182)	15	0.12	2	0.06	0.53 (0.45, 0.62)***	0.50 (0.11, 2.19)
Cervical (180)	30	0.24	3	0.09	0.40 (0.34, 0.47)***	0.45 (0.14, 1.47)
Ovary (183)	14	0.11	0	0.00	—	—
Prostate (185)	5	0.04	3	0.09	2.38 (2.14, 2.65)***	1.97 (0.45, 8.54)
Bladder (188)	14	0.11	3	0.09	0.85 (0.75, 0.97)*	0.81 (0.23, 2.84)
Kidney (189)	18	0.14	5	0.16	1.10 (0.98, 1.24)	1.00 (0.37, 2.72)
Thyroid (193)	20	0.16	52	1.62	10.3 (9.31, 11.5)***	10.4 (6.18, 17.4)***
Hematologic (200–208)	25	0.20	3	0.09	0.48 (0.41, 0.56)***	0.48 (0.14, 1.59)
Others	33	0.26	6	0.19	0.72 (0.63, 0.82)***	0.70 (0.29, 1.67)

[a]Incidence rate (per 1000 person-years).
[b]Multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, and hyperlipidemia.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4. Hazard Ratio for Outcome Compared Between GD Cohort and Non-GD Cohort by Follow-Up Duration

	Non-GD cohort			*GD cohort*				
Follow-up time (years)	*Event*	*PY*	*Rate*[a]	*Event*	*PY*	*Rate*[a]	*IRR [CI]*	*Adjusted HR*[b] *[CI]*
Breast								
≤3	33	53,834	0.61	17	13,471	1.26	2.06 (1.87, 2.27)***	2.03 (1.13, 3.67)*
3–6	29	38,658	0.75	9	9743	0.92	1.23 (1.09, 1.39)***	1.21 (0.57, 2.56)
6–9	25	24,027	1.04	8	6128	1.31	1.25 (1.09, 1.45)**	1.31 (0.59, 2.92)
>9	10	11,104	0.90	5	2799	1.79	1.98 (1.64, 2.40)***	1.94 (0.66, 5.67)
Thyroid								
≤3	10	53,834	0.19	39	13,471	2.90	15.6 (13.9, 17.5)***	16.0 (7.95, 32.1)***
3–6	4	38,658	0.10	7	9743	0.72	6.94 (6.18, 7.80)***	6.26 (1.82, 21.5)**
6–9	4	24,027	0.17	4	6128	0.65	3.92 (3.43, 4.49)***	3.57 (0.86, 14.8)
>9	2	11,104	0.18	2	2799	0.71	3.97 (3.27, 4.82)***	3.89 (0.55, 27.6)

[a]Incidence rate (per 1000 person-years).
[b]Multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, and hyperlipidemia.
*$p < 0.05$, **$p < 0.01$; ***$p < 0.001$.

comparison cohort (IRR = 1.44, 1.23, 1.60, 2.38, and 10.30 respectively). After adjusting for sex, age, and comorbidities, the HRs for developing breast and thyroid cancer were 1.58- and 10.40-fold higher for patients with GD. Furthermore, the analysis of HRs for developing breast and thyroid cancer was stratified by treatment time (Table 4). The incidence density rates were significantly higher in the first three years, that is, 2.06 and 15.6 per 1000 person-years in breast and thyroid cancer with GD respectively. Specifically, a 16-fold hazard of developing thyroid cancer in the first three years existed in the GD cohort compared to the non-GD cohort [CI = 7.95–32.1].

Discussion

This study used a comprehensive national database to investigate the incidence of cancer in a group of 32,140 GD patients. A one-to-four comparison was made to 127,623 controls randomly frequency matched for age, sex, and index year, with adjustments for baseline comorbidities that may cause a predisposition to cancer, including diabetes mellitus, hypertension, and hyperlipidemia. GD patients were more likely to be diagnosed subsequently with cancer of the thyroid and breast, with an aHR of 10.4 and 1.58 respectively. Knowledge of this increased cancer risk is valuable in the medical prevention and care of patients with GD. In this study, the older GD cohort had a higher risk of developing cancer compared with the younger cohort. The aHR was high for subsequent thyroid and breast cancer for GD patents within six and three years respectively. In addition, study subjects with diabetes had a 1.43-fold higher risk of developing cancer than those without diabetes.

An increased risk of thyroid cancer in GD patients has been previously reported (5,9,15,16). Graves' hyperthyroidism is caused by thyroid-stimulating antibodies (TSAb), which bind to and activate the thyrotropin receptor on thyroid cells (17). TSAb may play a role in determining the aggressiveness of thyroid cancer in GD patients (15). Thyroid carcinoma can be associated with various types of hyperthyroidism, ranging from 2.3% to 19% (9). A study report indicated a high prevalence of local advanced thyroid cancer in patients with hyperthyroidism (9). Careful evaluation of GD patients is always necessary to exclude the presence of associated malignancies and to determine the most appropriate therapeutic plan.

Breast cancer is the most common type of cancer in women. The thyroid follicular and lactating breast cells accumulate iodine by an active transport mechanism at the basolateral membrane mediated by the sodium–iodide symporter (NIS) (18,19), and iodine oxidization in the alveolar mammary cells is performed by lactoperoxidase, which is immunologically similar to the thyroperoxidase of in the thyroid gland (20). Certain reports have demonstrated an increased prevalence of autoimmune thyroid disease in patients with breast cancer (18,21–23).

The crosstalk between the thyroid and mammary glands primarily involves the triiodothyronine (T3) and thyroxine (T4) pathways, and activation of thyroid hormone receptors of the mammary gland induces differentiation and lobular growth in an estrogen-like manner (24,25). High T3 or T4 levels were positively associated with a high risk of breast cancer (10,23,26–28). However, the underlying mechanisms must still be elucidated. Additional large unbiased population-based studies are required to confirm our findings.

In order to examine whether patients with Graves' disease had more medical input and whether other diseases may have been recognized as they were under regular medical surveillance, we compared the difference in having breast cancer screening between women with and without Graves' disease. There was no difference in the percentage of having mammographies between these two groups. Therefore, we conclude that the higher subsequent cancer risk in Graves' disease patients is not due to a higher degree of medical attention or regular medical surveillance among this population.

Our study has a few limitations. First, the National Health Insurance Research Database (NHIRD) does not provide detailed patient information, such as smoking habits, alcohol consumption, body mass index (BMI), physical activity, socioeconomic status, and family history of cancer. These are major risk factors for numerous cancer types. Second, evidence derived from a cohort study is generally of lower methodological quality than that derived from randomized trials because a cohort study design is subject to bias related to

adjustments for confounders. Despite our meticulous study design, including adequate control of confounding factors, bias could remain because of possible unmeasured or unknown confounders. Third, the diagnoses recorded in NHI claims are used primarily for administrative billing, and are not, therefore, subject to verification for scientific purposes. We were unable to contact the patients directly to obtain additional information because of the anonymity ensured by the identification numbers. In addition, our analyses excluded cancer patients prior to this study. This omission could have resulted in an underestimation of GD patients, and may have weakened our observed association. However, the data we obtained on GD therapy and cancer diagnoses were highly reliable. Furthermore, in the study sample, only a few (0.14%) GD patients underwent thyroidectomy. Thus, we were unable to verify whether thyroidectomy as therapy for hyperthyroidism was associated with the diagnosis of thyroid cancer in this data set.

Despite these limitations, our study provides important information. This is the first large-scale nationwide cohort study of cancer and GD conducted in an Asian population. Patients with GD, particularly older patients, are at risk for the development of thyroid and breast cancer compared with the general population. In addition, an increased relative risk of developing thyroid and breast cancer was observed in patients with GD in the subsequent six and three years respectively. Therefore, the management of older GD patients requires close follow-up for surveying the possibility of cancer occurrence. Strategies helping to prevent thyroid and breast cancer (like ultrasound and/or mammography survey) are therefore recommended for these patients.

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Author Disclosure Statement

The authors declare that they have no conflicts of interest.

References

1. Weetman AP 2000 Graves' disease. N Engl J Med **343:**1236–1248.
2. Cooper DS 2003 Hyperthyroidism. Lancet **362:**459–468.
3. Vanderpump MPJ, Tunbridge WMG 1999 The epidemiology of autoimmune thyroid disease. In: Volpé R (ed) Autoimmune Endocrinopathies. Vol. 15 of Contemporary Endocrinology. Humana Press, Totowa, NJ, pp. 141–162.
4. Jacobson DL, Gange SJ, Rose NR, Graham NM 1997 Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol **84:**223–243.
5. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K 2010 Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. Br J Cancer **102:** 1397–1399.
6. de la Cruz-Merino L, Grande-Pulido E, Albero-Tamarit A, Codes-Manuel de Villena ME 2008 Cancer and immune response: old and new evidence for future challenges. Oncologist **13:**1246–1254.
7. Fiore E, Giustarini E, Mammoli C, Fragomeni F, Campani D, Muller I, Pinchera A, Giani C 2007 Favorable predictive value of thyroid autoimmunity in high aggressive breast cancer. J Endocrinol Invest **30:**734–738.
8. Giustarini E, Pinchera A, Fierabracci P, Roncella M, Fustaino L, Mammoli C, Giani C 2006 Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol **154:**645–649.
9. Pazaitou-Panayiotou K, Perros P, Boudina M, Siardos G, Drimonitis A, Patakiouta F, Vainas I 2008 Mortality from thyroid cancer in patients with hyperthyroidism: the Theagenion Cancer Hospital experience. Eur J Endocrinol **159:** 799–803.
10. Tosovic A, Becker C, Bondeson AG, Bondeson L, Ericsson UB, Malm J, Manjer J 2012 Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. Int J Cancer **131:**2126–2133.
11. Wong GWK and Cheng PS 2001 Increasing incidence of childhood Graves' disease in Hong Kong: a follow-up study. Clin Endocrinol **54:**547–550.
12. Kraimps JL, Bouin-Pineau MH, Mathonnet M, De Calan L, Ronceray J, Visset J, Marechaud R, Barbier J 2000 Multicentre study of thyroid nodules in patients with Graves' disease. Br J Surg **87:**1111–1113.
13. Cheng TM 2009 Taiwan's national health insurance system: high value for the dollar. In: Okma KGH, Crivelli L (eds) Six Countries, Six Reform Models: Their Healthcare Reform, Experience of Israel, the Netherlands, New Zealand, Singapore, Switzerland and Taiwan. World Scientific Publishing Co., Hackensack, NJ, pp. 171–204.
14. Israel RA, Converse ME, Davis JB, Egelston EM, Green D, Johnson K, Kincaid WH, Meads MS, Price E, Savitt HL, Slee VN, Warden GL, Waterstraat M, Weigel KM, Zintel HA; National Center for Health Statistics 2011 International Classification of Diseases, 9th Revision, Clinical Modification, 6th ed. Centers for Disease Control and Prevention, Atlanta, GA. Available at www.cdc.gov/nchs/icd/icd9cm.htm
15. Belfiore A, Garofalo MR, Giuffrida D, Runello F, Filetti S, Fiumara A, Ippolito O, Vigneri R 1990 Increased aggressiveness of thyroid cancer in patients with Graves' disease. J Clin Endocrinol Metab **70:**830–835.
16. Majima T, Komatsu Y, Doi K, Shigemoto M, Takagi C, Fukao A, Kojima M, Tamaki H, Ito J, Nakao K 2005 Anaplastic thyroid carcinoma associated with Graves' disease. Endocr J **52:**551–557.
17. Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM 1998 The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. Endocr Rev **19:**673–716.
18. Smyth PP, Shering SG, Kilbane MT, Murray MJ, McDermott EW, Smith DF, O'Higgins NJ 1998 Serum thyroid peroxidase autoantibodies, thyroid volume, and outcome in breast carcinoma. J Clin Endocrinol Metab **83:**2711–2716.
19. Dai G, Levy O, Carrasco N 1996 Cloning and characterisation of the thyroid iodide symporter. Nature **379:**458–460.
20. Fierabracci P, Pinchera A, Campani D, Pollina LE, Giustarini E, Giani C 2006 Association between breast cancer and autoimmune thyroid disorders: no increase of lymphocytic infiltrates in breast malignant tissues. J Endocrinol Invest **29:**248–251.
21. Ito K, Maruchi N 1975 Breast cancer in patients with Hashimoto's thyroiditis. Lancet **2:**1119–1121.

22. Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E, Pinchera A 1996 Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. J Clin Endocrinol Metab **81:**990–994.
23. Turken O, NarIn Y, DemIrbas S, Onde ME, Sayan O, KandemIr EG, YaylacI M, Ozturk A 2003 Breast cancer in association with thyroid disorders. Breast Cancer Res **5:** R110–113.
24. Gonzalez-Sancho JM, Garcıa V, Bonilla F, Munoz A 2003 Thyroid hormone receptors/THR genes in human cancer. Cancer Lett **192:**121–132.
25. Conde I, Paniagua R, Zamora J, Blánquez MJ, Fraile B, Ruiz A, Arenas MI 2006 Influence of thyroid hormone receptors on breast cancer cell proliferation. Ann Oncol **17:**60–64.
26. Cengiz O, Bozkurt B, Unal B, Yildirim O, Karabeyoglu M, Eroglu A, Koçer B, Ulaş M 2004 The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women. J Surg Oncol **87:**19–25.
27. Saraiva PP, Figueiredo NB, Padovani CR, Brentani MM, Nogueira CR 2005 Profile of thyroid hormones in breast cancer patients. Braz J Med Biol Res **38:**761–765.
28. Tosovic A, Bondeson AG, Bondeson L, Ericsson UB, Malm J, Manjer J 2010 Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. Breast Cancer Res **12:**R33.

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