Do Thyroid Disorders Increase the Risk of Breast Cancer?[1]

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Abstract

The objective of this study was to determine whether thyroid disorders or treatment of such disorders affects the risk of breast cancer. Subjects aged 35–64 years were participants in the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study, a population-based, case-control study of invasive breast cancer that was carried out at five sites in the United States. In-person interviews were completed for 4575 women (cases) with breast cancer (2953 white and 1622 black) and 4682 control women (3021 white and 1661 black). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multiple logistic regression methods. Models included adjustment for age (5-year age groups), race (white or black), and site. A history of any thyroid disorder (OR = 1.1, 95% CI = 0.9–1.2) was not associated with breast cancer risk. Only women with a history of thyroid cancer had an increased risk, but this was restricted to parous women (parous OR = 3.4, 95% CI = 1.5–8.1; nulliparous OR = 0.5, 95% CI = 0.04–5.1). Breast cancer risk was not associated with treatment for thyroid disorders. There was no statistical interaction between thyroid disorders, thyroid treatments, and race, menopausal status, or parity. We found no association between thyroid disorders or their associated treatments and the risk of breast cancer.

Introduction

A relationship between thyroid disease and risk of breast cancer is supported by experiments suggesting a role for thyroid hormones (1), insulin, and insulin-like growth factor-1 (2) on the regulation of breast epithelial cell growth. Even so, evidence regarding a relationship between diseases of the thyroid and breast cancer risk is, on the whole, not compelling (3–13). Several epidemiological studies have found no significant relationship between either thyroid disorders (3) or treatment for thyroid disorders (12) and breast cancer risk, but others have found modest effects for hyperthyroidism (13), thyroid hormone treatment (4), and radioactive iodine treatment (13). In addition, a protective effect was found for untreated goiters (4). Limitations in the literature investigating relationships between breast cancer and thyroid disorders include small samples (4) and a lack of information of the specific types of thyroid disorder (6) or treatment (3).

We examined whether thyroid disorders and/or treatment of these disorders affect the risk of breast cancer. We used data from a large case-control study of invasive breast cancer in which participants were asked about their history of several medical conditions potentially related to use of female hormones. That study ascertained data on specific thyroid conditions and treatments, as well as the timing of disease onset and duration of treatment.

Materials and Methods

Participants were enrolled in the National Institute of Child Health and Human Development Women's CARE[4] Study, a population-based, case-control study that was carried out at five sites in the United States. Four of the sites were affiliated with cancer registries funded through the National Cancer Institute's SEER Program (Atlanta, Detroit, Los Angeles, and Seattle/Puget Sound); the fifth site had no SEER affiliation (Philadelphia; Ref. 14).

As described previously in detail, United States-born white and black women aged 35–64 years who were newly diagnosed with invasive breast cancer in July 1994 to April 1998 were eligible to serve as cases in the Women's CARE Study (14). Cases were identified through rapid ascertainment

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[4] The abbreviations used are: CARE, Contraceptive and Reproductive Experiences; SEER, Surveillance, Epidemiology, and End Results; OR, odds ratio; BMI, body mass index; HRT, hormone replacement therapy; CI, confidence interval.

systems at the SEER-affiliated sites and by field staff in Philadelphia. Controls were chosen from the same counties as the cases, selected by random-digit dialing, and were frequency matched to cases based on 5-year age groups, race, and geographic site. Younger cases, and black cases and controls were oversampled to approximate a uniform distribution across age and race groups with the goal of efficiently assessing effect modification.

Exposure information was obtained during in-person interviews conducted by trained interviewers. Completed interviews were obtained for 4575 of the 5982 eligible cases (76.5%) and 4682 of the 5956 randomly selected controls (78.6%). The interview instrument included detailed questions on the previous use of oral contraceptive pills, HRT, fertility drugs, and other hormones. It also included questions on many other potential risk factors for breast cancer, including: (*a*) reproductive; (*b*) exercise; (*c*) health and family histories; (*d*) smoking and alcohol exposures; (*e*) demographics; and (*f*) medical history. Exposure information was collected for the time period preceding a set reference date, which was the date of diagnosis for cases and of initial household screening for controls.

All respondents were asked, "Before (reference date), did a doctor or other health professional ever tell you that you had a thyroid problem or any condition requiring thyroid medication or treatment?" Those who answered "yes" were shown a list of thyroid-associated conditions, including: (*a*) Graves' disease; (*b*) Hashimoto's disease (chronic thyroiditis); (*c*) overactive (hyperactive) thyroid; (*d*) under active (hypoactive); (*e*) goiter; (*f*) nodules; (*g*) cancer; and (*h*) other conditions. They were then asked, "What type of problem or condition was this?" Subsequently, respondents were asked, "Before (reference date), have you been hospitalized, had surgery, been prescribed medications, or been treated for any thyroid problem or condition?" Those who answered "yes" were shown a list of thyroid-associated medications, including: (*a*) thyroid USP or equivalent; (*b*) Synthroid or equivalent; (*c*) thyroid gland inhibitors; and (*d*) other medications. They were also shown a list of thyroid-associated procedures, including: (*a*) thyroid surgery; (*b*) radioactive iodine treatment; (*c*) X-ray or radiation treatment; and (*d*) other treatments. We evaluated whether a history of a thyroid disorder was associated with breast cancer risk and whether risk varied by time since first diagnosis, type of thyroid disorder, or treatments and duration of treatments.

ORs and 95% CIs were calculated using unconditional multivariate logistic regression methods (15). Models included adjustment for age (5-year groups), race (white or black), and study site. We examined other variables as potential confounding factors. None of the factors we considered changed the ORs by ≥10%, including: (*a*) first-degree family history of breast cancer (except in the analysis of thyroid cancer); (*b*) BMI at reference date minus 5 years; (*c*) number of full-term pregnancies (>26 weeks); (*d*) age at first full-term pregnancy; (*e*) education; (*f*) income; (*g*) age at menarche; (*h*) menopausal status; (*i*) mammogram screening history in the past 2 years; (*j*) alcohol consumption; (*k*) smoking history; (*l*) duration of oral contraceptive use; and (*m*) duration of HRT. In analyzing the association between preexisting thyroid cancer and risk of breast cancer, we adjusted for family history of breast cancer because the adjusted and unadjusted effect estimates as noted differed by ≥10%. Stratified analyses were conducted using likelihood tests for heterogeneity to the regression models to assess effect modification by menopausal status, race, and parity (16).

Results

Demographic and risk factor characteristics of 4575 cases and 4682 controls in the Women's CARE Study, which have been described elsewhere (14), are presented in Table 1. The study population was approximately one-third black, and just over half was premenopausal. On average, controls in our study had more full-term pregnancies than did the cases and were less likely than the cases to have had a first-degree family history of breast cancer.

The relationship between a history of thyroid disorders and risk of breast cancer is shown in Table 2. A history of any thyroid disorder was not associated with breast cancer (OR = 1.1, 95% CI = 0.9–1.2). There were no significant associations by time since first diagnosis of any of the thyroid disorders. An increased risk of breast cancer was detected among women with a history of thyroid cancer (OR = 2.7, 95% CI = 1.2–5.9), although this risk was restricted to parous women (OR = 3.4, 95% CI = 1.5–8.1). On the basis of the small number of women (one case and two controls), thyroid cancer was not found to be associated with risk of breast cancer for nulliparous women. We observed no association between breast cancer risk and type of thyroid medication, duration of thyroid medication use, or exposure to other thyroid procedures or treatments (Table 3). Finally, no statistical interaction was seen by race, menopausal status, or parity (data not shown).

Discussion

The largely negative results of this study support the majority of reports in the literature and provide additional reassurance that neither disorders of the thyroid nor treatment for these conditions substantially alters the risk for breast cancer among women aged 35–64 years. This study was large and population based, providing an advantage over studies that are hospital based (8, 10). Although two other studies included some data on minority populations (12, 13), no other investigations had a sample large enough to evaluate differences in risk by race. In addition, we tried to evaluate issues not completely addressed in previous publications, such as the potential elevation in risk associated with specific thyroid disorders and treatments and the recency of diagnoses and duration of treatments. This is potentially important because these conditions probably operate via different mechanisms, and group analysis could mask true findings. Limitations inherent in the design of a case-control study, such as selection bias, have been discussed previously, although our high-response rates argue against much selection bias (14). Other limitations that are specific to our analysis include the lack of provisions to confirm diagnoses of medical conditions other than breast cancer and the fact that subject recall was the only basis for data on previous medications or treatments.

Even though there is *in vitro* evidence for an effect of thyroid hormones on breast epithelial proliferation (1, 17, 18), the epidemiological literature provides little support for an association between thyroid disorders and breast cancer risk (3, 6, 12). In one large population-based, case-control study, there was a protective effect associated with untreated goiters (OR = 0.34, 95% CI = 0.1–0.8; Ref. 4), but this finding was based on small numbers. Other researchers have not identified associations for a history of goiters or untreated goiters (8), and analysis of our data supports these earlier findings (data not shown; Ref. 13). Data from another hospital-based, case-control study showed a small protective effect for thyroid adenomas diagnosed among premenopausal women (OR = 0.4, 95% CI = 0.1–0.7) or among women aged <35 (OR = 0.4,

Table 1 Demographic and risk factor characteristics of 4575 cases and 4682 controls in the Women's CARE Study

Characteristic	Cases (n = 4575)		Controls (n = 4682)	
	n	%	*n*	%
Age (yrs)				
35–39	689	15.1	666	14.2
40–44	758	16.6	832	17.8
45–49	782	17.1	857	18.3
50–54	844	18.5	825	17.6
55–59	770	16.8	801	17.1
60–64	732	16.0	701	15.0
Race				
White	2953	64.5	3021	64.5
Black	1622	35.5	1661	35.5
Study site				
Atlanta	881	19.3	895	19.1
Detroit	679	14.8	779	16.6
Los Angeles	1242	27.2	1255	26.8
Philadelphia	707	15.5	736	15.7
Seattle	1066	23.3	1017	21.7
Education[a]				
Less than high school	399	8.7	444	9.5
High school	1335	29.2	1350	28.8
Some college	1483	32.4	1495	31.9
College graduate or more	1357	29.7	1393	29.8
BMI (kg/m^2)[b]				
<21.5	1130	24.8	1104	23.7
21.5 to <28.5	2409	53.0	2413	51.8
28.5+	1011	22.2	1145	24.6
Age at menarche (yrs)[c]				
<12	1197	26.2	1262	27.0
12–13	2528	55.4	2464	52.7
>13	840	18.4	950	20.3
Number of full-term pregnancies[d,e]				
0	890	19.5	805	17.2
1	770	16.8	717	15.3
2	1371	30.0	1355	29.0
3+	1541	33.7	1796	38.4
Age at first full-term pregnancy (yrs)[f]				
<20	1046	28.4	1191	30.8
20–24	1368	37.1	1461	37.8
25–29	777	21.1	718	18.6
≥30	492	13.4	497	12.9
Menopausal status[g]				
Premenopausal	2116	52.4	2061	50.4
Postmenopausal	1924	47.6	2029	49.6
Use of oral contraceptives[h]				
Never	1042	22.8	990	21.2
<6 months	512	11.2	508	10.9
6 mos to <5 yrs	1488	32.6	1612	34.5
≥5 years	1525	33.4	1566	33.5
HRT for menopausal use[e,i]				
Never	2837	62.1	2749	58.7
<6 months	318	7.0	388	8.3
6 mos to <5 yrs	610	13.3	716	15.3
≥5 years	807	17.7	827	17.7
First degree family history of breast cancer[e,j]				
No	3616	82.3	4050	89.9
Yes	778	17.7	453	10.1

[a] Data missing for one case.
[b] Quetelet's Index calculated as weight (kg)/height (m)^2 and based on weight 5 years before the participant's reference date. Data were missing for 26 cases and 21 controls.
[c] Data were missing for 10 cases and 6 controls.
[d] Includes all pregnancies lasting >26 weeks. Data were missing for three cases and nine controls.
[e] Statistically significant with a $P < 0.01$.
[f] Data were missing for 2 cases and 10 controls.
[g] Unknown or unable to classify menopausal status for 535 cases and 592 controls.
[h] Data were missing for three cases and four controls.
[i] Data were missing for one case and one control.
[j] First-degree family includes mother, full sister(s), and daughter(s). Data were missing for 181 cases and 179 controls who were either adopted or had unknown family history of breast cancer.

Table 2 Relationship between history of thyroid disorders and breast cancer risk

	Cases (n = 4571)		Controls (n = 4677)		OR[a]	95% CI
	n	%	*n*	%		
History of thyroid disorder[b]						
Never	3751	82.1	3876	82.9	1.0	
Ever	820	17.9	801	17.1	1.1	0.9–1.2
Years since first diagnosis of thyroid disorder[c]						
0 to <10	292	6.4	283	6.1	1.1	0.9–1.2
10 to <25	279	6.1	288	6.2	1.0	0.8–1.2
≥25	332	7.3	373	8.0	0.9	0.7–1.03
Type of thyroid disorder						
Graves disease	39	0.9	33	0.7	1.2	0.8–1.9
Hashimoto's disease	34	0.7	37	0.8	0.9	0.6–1.5
Hyperactive	125	2.7	141	3.0	0.9	0.7–1.1
Hypoactive	465	10.2	530	11.3	0.9	0.8–1.02
Goiter	120	2.6	119	2.5	1.0	0.8–1.3
Nodules	71	1.6	63	1.4	1.1	0.8–1.6
Thyroid cancer[d]	23	0.5	10	0.2	2.7	1.2–5.9
Other problem(s)	42	0.9	52	1.1	0.8	0.5–1.2

[a] OR was relative to never having had a thyroid disorder, adjusted for age, race, and study site.
[b] Excludes nine women that did not know if they had a history of a thyroid disorder.
[c] Five cases and five controls were missing because of unknown diagnosis year.
[d] OR adjusted for age, race, study site, and first-degree family history of breast cancer.

95% CI = 0.2–0.8; Ref. 8). Our study was not able to evaluate the risk of breast cancer for women aged <35 years. However, we found no association for thyroid adenomas (nodules) among premenopausal women (OR = 1.1, 95% CI = 0.6–2.1). Others who have evaluated time since diagnosis of thyroid disease found no significant effects (3, 12, 13). One other report found a relationship between hyperthyroidism and breast cancer risk, but it was based on only 17 cases and 19 controls (OR = 2.2, 95% CI = 1.1–4.4; Ref. 13), and this finding has not been replicated by us or by others (3, 4, 8). Thus, although some studies suggest a protective effect of goiters or adenomas, our results, as well as much of the published literature on this issue, do not substantiate these findings.

Epidemiological support is also scant for an association between treatments for thyroid disorders and breast cancer risk (3, 6, 8, 10). One study showed a decrease in risk for women with untreated goiters and an increase in risk after 5–9 years of thyroid medication use, but no time trends were seen, and no significant effects were observed for euthyroid women who used thyroid medications for other reasons (4). Our results are consistent with those from other large studies in which no significant effects have been found for specific thyroid treatments, particularly I^{131} and X-ray treatment, on breast cancer risk (9, 11, 13).

Our finding of a significant association between a history of thyroid cancer and breast cancer risk has been reported by others (19, 20). In our study, the direction and strength of this association varied by parity, although the interaction was not found to be statistically significant and could very well have been attributable to chance. The relationship between thyroid cancer and breast cancer may reflect the influence of shared hormonal or genetic factors and should be studied further.

In conclusion, although there is laboratory evidence that thyroid hormones, insulin, and other growth factors can influ-

Table 3 Relationship between use of thyroid medications and procedures and breast cancer risk[a]

	Case (n = 4502)		Control (n = 4604)		OR[b]	95% CI
	n	%	n	%		
Thyroid medications						
Never	3791	84.2	3867	84.0	1.0	
Ever	711	15.8	737	16.0	1.0	0.9–1.1
Type of medications[c]						
Thyroid USP/equivalent						
Ever[d]	87	1.9	93	2.0	0.9	0.7–1.3
≤1 yr	21	0.5	23	0.6	0.9	0.5–1.7
>1 yr, ≤10 yrs	32	0.8	33	0.8	1.0	0.6–1.6
>10 yrs	34	0.9	35	0.9	1.0	0.6–1.6
Synthyroid/equivalent						
Ever[e]	499	11.1	537	11.7	0.9	0.8–1.1
≤1 yr	81	1.9	100	2.3	0.8	0.6–1.1
>1 yr, <10 yrs	232	5.4	244	5.6	1.0	0.8–1.2
>10 yrs	184	4.3	189	4.3	1.0	0.8–1.2
Thyroid gland inhibitor						
Ever	23	0.5	26	0.6	0.9	0.5–1.6
≤1 yr	16	0.4	14	0.4	1.1	0.6–2.4
>1 yr	7	0.2	12	0.3	0.6	0.2–1.5
Other medication(s)						
Ever[f]	22	0.5	25	0.5	0.9	0.5–1.6
≤1 yr	12	0.3	8	0.2	1.5	0.6–3.7
>1 yr	9	0.2	17	0.4	0.6	0.2–1.3
Other thyroid procedures[g]						
Never	4333	94.9	4433	95.1	1.0	
Ever	231	5.0	231	5.1	1.0	0.8–1.2
Types						
Thyroid surgery	136	3.0	114	2.4	1.2	0.9–1.6
Radioactive iodine	102	2.2	105	2.3	1.0	0.8–1.3
X-ray/radiation	29	0.6	35	0.8	0.9	0.5–1.4
Other treatment(s)	20	0.4	20	0.4	1.1	0.6–2.0

[a] Data were missing for 73 cases and 78 controls.
[b] ORs were relative to never using any thyroid medications (except for other thyroid procedures), adjusted for age, race, and study site.
[c] Some women took more than one type of thyroid medications. These data reflects duration of use.
[d] Duration of USP use was unknown for two women.
[e] Duration of synthyroid use was unknown for six women.
[f] Duration of other thyroid medication use was unknown for one woman.
[g] Some women received more than one procedure. OR was relative to never having any procedures.

ence the growth and regulation of breast epithelial cells *in vivo*, we found no evidence of a positive association between risk of breast cancer and thyroid disease or its treatment, among women aged 35–64 years, except for thyroid cancer.

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