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Breast Cancer Risk in Postmenopausal Women with Medical History of Thyroid Disorder in the Women's Health Initiative

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Background: The association between thyroid disorders and breast cancer remains controversial, in part, due to small cohort sizes and inconsistent findings. We investigated this association in postmenopausal women to determine whether hyper- or hypothyroidism is associated with the risk of developing breast cancer and to determine whether menopausal hormone therapy (MHT) further modifies the risk.
Methods: We conducted a prospective cohort study of multiethnic U.S. postmenopausal women aged 50 to 79 years enrolled in both clinical trial and observational study arms between 1993 and 1998 and followed up through February 28, 2017. Development of invasive breast cancer after enrollment was recorded and a history of hyper- or hypothyroidism before the diagnosis of breast cancer was identified. The effect modification by MHT in both study arms was analyzed. All statistical tests were two sided.
Results: Among a total of 134,122 women who were included in our study, 8137 participants developed invasive breast cancer during the follow-up period. There was a significant inverse association of invasive breast cancer among women with a history of hypothyroidism (hazard ratio [HR] 0.91, confidence interval [95% CI] 0.86–0.97) and among women who had taken levothyroxine [HR 0.89, 95% CI 0.82–0.96]. Evaluating effect modification by MHT use, the inverse association between hypothyroidism treated with thyroid replacement medications and breast cancer risk was strongest in non-MHT users [HR 0.80, 95% CI 0.69–0.93]. The results did not significantly differ by race/ethnicity. Although a history of hyperthyroidism was associated with an increased risk of invasive breast cancer [HR 1.11, 95% CI 0.91–1.35], this finding did not reach statistical significance. We did not see significant differences in the breast cancer Surveillance, Epidemiology, and End Results stages, histologic types, morphologic grades, or receptor status (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) according to thyroid disorder status.
Conclusions: Compared with women with no history of thyroid disorder, hypothyroidism was associated with a lower risk of breast cancer. This was mainly seen among those who received thyroid replacement therapy and had never used MHT. Among the treatment options for hypothyroidism, levothyroxine had the strongest inverse association with breast cancer risk.

Keywords: thyroid disorder, hypothyroidism, hyperthyroidism, breast cancer, postmenopausal

Introduction

One in eight women will develop breast cancer in their lifetime, making it the most commonly diagnosed cancer in this population (1,2). Estrogens are believed to play a key role in the development of breast cancer (3). *In vitro*, high levels of thyroid hormone are found to have estrogen-like effects on breast carcinoma cells and may promote the development of breast cancer by binding to the estrogen receptor (ER) (4–7).

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The association between thyroid disorders and breast cancer has been studied in the past with mixed results. Most of the articles published to date have relied on studies of relatively small sample sizes (6,8–17). A recent systematic review and meta-analysis that included 13 population-based studies with 24,808 participants through June 2016 found that neither hypothyroidism nor hyperthyroidism was related to the risk of breast cancer (18). Weng *et al.*, using the Taiwanese national database that included 103,466 Asian women, found that women younger than 55 years with a history of hyperthyroidism had a 16% higher risk of developing breast cancer compared with those without a history of thyroid disorder. A history of hypothyroidism was also found to be associated with a 19% higher risk, without stratification by age (19). A study utilizing the national registry in Denmark by Sogaard *et al.* also examined this association without age stratification and found a similar result for hyperthyroidism, but not for hypothyroidism (9).

With respect to other hormonal factors associated with breast cancer risk, menopausal hormone therapy (MHT, referring to unopposed estrogen and estrogen combined with progestin) and the risk of breast cancer in postmenopausal women have been investigated for more than a decade. Most of the studies have found some increased risk of breast cancer in women who took estrogen combined with progestins (20,21).

We hypothesized that the association between thyroid disorders and breast cancer risk may be most apparent among nonusers of MHT, since MHT has been shown to increase this risk. Interestingly, there have been no studies examining the role of thyroid disease, MHT, and breast cancer risk. The aim of this study was to assess the association between thyroid disorders and breast cancer risk in postmenopausal women and to evaluate the effect modification of MHT use in a longitudinal cohort of 161,808 postmenopausal women in both the Clinical Trial (CT) and Observational Study (OS) arms of the Women's Health Initiative (WHI), one of the largest prospective studies to date.

Methods

Study population

The WHI consists of an OS cohort ($N=93,676$) (OS) and three CTs ($N=68,132$) (CT)—which includes MHT, dietary modification (DM), and calcium and vitamin D supplement (CaD) trials (22,23). The WHI enrolled postmenopausal women, ages 50 to 79 years, from major ethnic groups who had a predicted survival of at least 3 years. Participants were recruited from 40 clinical centers in the United States between October 1, 1993, and December 31, 1998; they were initially followed through March 2005. Consent for recontact for follow-up and medical record release was obtained from the participants in two extension studies (2005–2010 and 2010–2020) (24). We included WHI participants (both OS and CT groups) whose medical history was negative for any type of cancer at enrollment; among this group, we excluded participants if they developed another malignancy before the diagnosis of breast cancer. We also excluded those with missing data for specific exposures, those lost to follow-up, those with carcinoma *in situ* (CIS) or unstaged invasive breast cancer, those who reported that they took thyroid medication but did not have a thyroid disorder diagnosis, and those whose breast cancer diagnosis was derived from death certificates (Fig. 1).

The National Institutes of Health Institutional Review Boards for all participating clinical sites approved the WHI protocols and consent forms. More information can be found at: https://clinicaltrials.gov/ct2/show/NCT00000611.

Exposure

Participants were asked the following questions at enrollment to determine whether or not they had a history of a thyroid disorder: ''Did a doctor ever say that you had a thyroid gland problem (not including thyroid cancer)?'' ''Do you have any of the following conditions? (Please mark 'No' or 'Yes' for each condition.)'' ''overactive thyroid'' or ''underactive thyroid.''

Data collection and definition

A self-reported medical history of overactive thyroid and/or underactive thyroid during the main study period (1993–2005) at enrollment was used as the exposure variable. Participants who reported having medical histories of both hyperthyroidism and hypothyroidism were defined as having mixed thyroid disorder.

Outcome

In brief, women were queried twice each year to determine whether they had been hospitalized or diagnosed with any of the clinical outcomes on a prespecified list, including breast cancer. Self-report of breast cancer was verified by medical record and pathology report review by centrally trained WHI physician adjudicators at each participating clinical center. Central adjudication and coding of histology, extent of disease, and ER and progesterone receptor (PR) status (positive or negative per local pathology report) were performed at the clinical coordinating center using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) coding system. Invasive breast cancer characteristics, including stages defined by SEER stages, histology types (ductal, lobular, ductal, and lobular), morphology grade (well, moderately, poorly differentiated, and anaplastic), and receptor status (ER; PR; human epidermal growth factor receptor 2, HER2) were compared by thyroid disorder types.

Statistical analyses

To compare the baseline characteristics between the group of 111,740 women with no history of thyroid disorder, the group of 1695 with a history of hyperthyroidism, the group of 19,735 with a history of hypothyroidism, and the group of 952 with a history of mixed thyroid disorder, we used analysis of variance for continuous variables and chi-square statistics for categorical variables. Cox proportional hazard models were used to calculate the hazard ratios (HRs) of thyroid disorders for invasive breast cancer risk. Two models stratified by MHT arm were applied in the analysis: model 1 was adjusted for age, and model 2 was adjusted for age, race/ethnicity, body mass index (BMI), the use of medications to treat hypothyroidism, smoking, alcohol intake, history of breast feeding, history of bilateral oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, history of obtaining a

mammogram, history of diabetes, and history and type of hormone therapy. We further stratified the analysis for invasive breast cancer risk and thyroid disorders by race/ethnicity (Caucasians, African Americans, Hispanics, and Asian or Pacific Islanders). Cox models by MHT type (both age adjusted and fully adjusted) (as model 2) were also examined. Nominal confidence intervals [95% CIs] and *p*-values were used to reflect statistical significance. The proportional hazard assumption was tested within each model through the use of an interaction term incorporating thyroid disorder and length of follow-up. In addition, a sensitivity analysis was conducted using thyroid medication in place

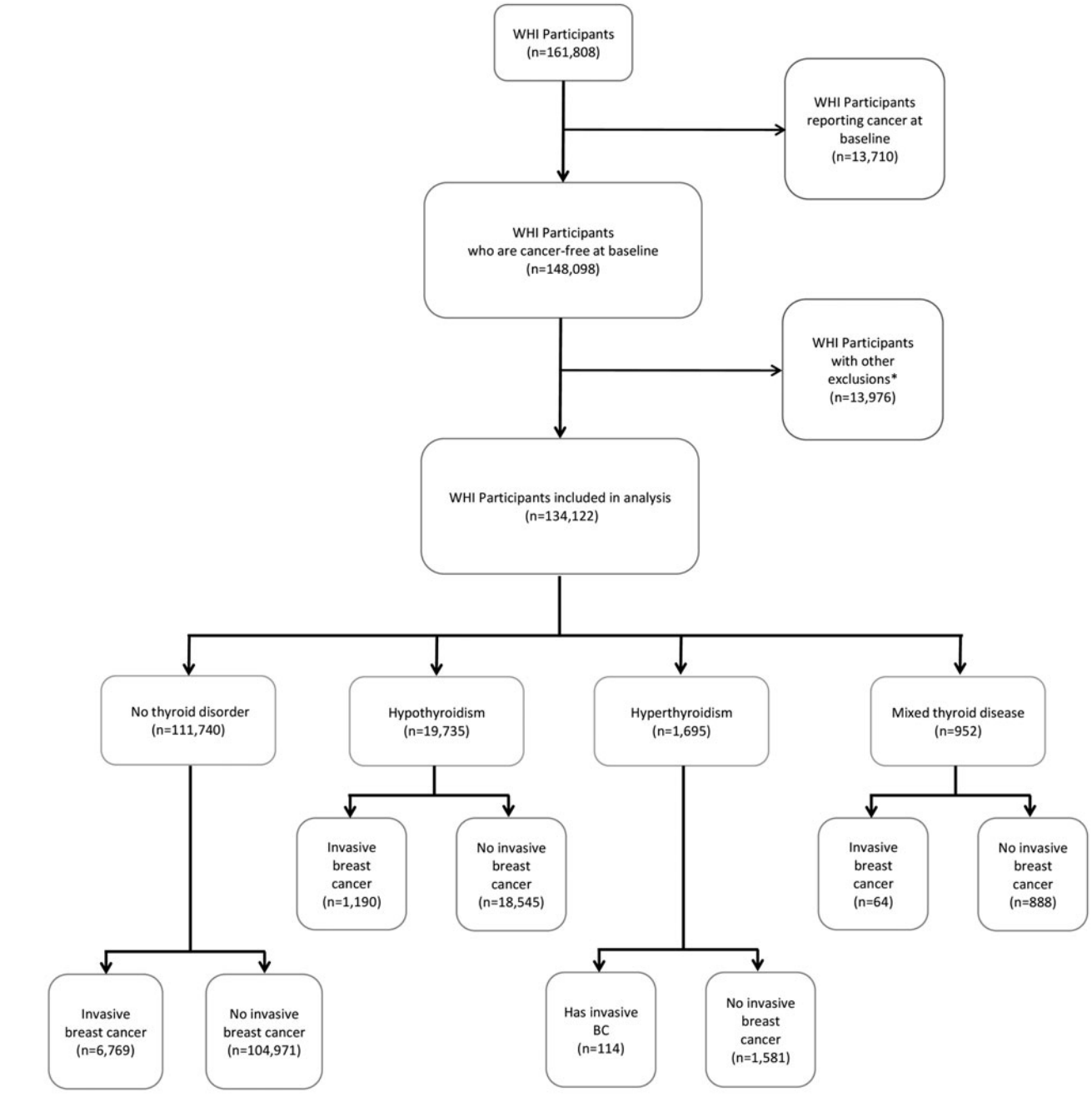

FIG. 1. Flow diagram.

Table 1. Demographic and Physiologic Characteristics

	Without history of thyroid disorder (n = 111,740)	*With history of hypothyroidism* (n = 19,735)	*With history of hyperthyroidism* (n = 1695)	*With history of mixed thyroid disorder* (n = 952)	p
WHI cohort					
CT participant	50,463 (45.2)	7814 (39.6)	666 (39.3)	386 (40.6)	<0.001
OS participant	61,277 (54.8)	11,921 (60.4)	1029 (60.7)	566 (59.5)	
Age (years)	62.8 (7.2)	63.9 (7.0)	63.4 (7.1)	63.1 (6.9)	<0.001
Race/ethnicity					
White (not of Hispanic origin)	90,589 (81.1)	18,127 (91.9)	1302 (76.8)	813 (85.4)	<0.001
Black or African American	11,175 (10.0)	643 (3.3)	255 (15.0)	67 (7.0)	
Hispanic/Latino	4924 (4.4)	442 (2.2)	42 (2.5)	24 (2.5)	
Asian or Pacific Islander	3268 (2.9)	261 (1.3)	63 (3.7)	35 (3.7)	
Other	1784 (1.6)	262 (1.3)	33 (2.0)	13 (1.4)	
Body mass index	27.9 (6.0)	28.8 (6.4)	26.9 (5.7)	27.8 (5.8)	<0.001
Current thyroid medications	0 (0.0)	12,382 (62.7)	55 (3.2)	730 (76.7)	<0.001
Hypothyroid medications	0 (0.0)	12,155 (61.6)	0 (0.0)	717 (75.3)	<0.001
T3 hypothyroidism medication	0 (0.0)	46 (0.2)	0 (0.0)	1 (0.1)	<0.001
T3/T4 hypothyroidism medication	0 (0.0)	655 (3.3)	10 (0.6)	26 (2.7)	<0.001
T4 hypothyroidism medication	0 (0.0)	11,483 (58.2)	0 (0.0)	692 (72.7)	<0.001
Hyperthyroidism medications	0 (0.0)	0 (0.0)	45 (2.7)	3 (0.3)	<0.001
Smoking					
Never	57,478 (51.4)	9415 (47.7)	796 (47.0)	410 (43.1)	<0.001
Past	44,978 (40.3)	8970 (45.5)	711 (42.0)	442 (46.4)	
Current	7842 (7.0)	1121 (5.7)	174 (10.3)	84 (8.8)	
Alcohol use	2.38 (4.87)	2.40 (5.00)	2.21 (4.76)	2.23 (5.06)	0.333
Any breastfeeding	56,605 (50.7)	10,460 (53.0)	827 (48.8)	438 (46.0)	<0.001
Duration of breastfeeding					
Never breastfed	53,894 (48.2)	9097 (46.1)	850 (50.2)	500 (52.5)	<0.001
1–6 Months	28,370 (25.4)	5264 (26.7)	439 (25.9)	220 (23.1)	
7–12 Months	12,234 (11.0)	2233 (11.3)	171 (10.1)	96 (10.1)	
13–23 Months	9484 (8.5)	1820 (9.2)	123 (7.3)	75 (7.9)	
24+ Months	6181 (5.5)	1091 (5.5)	90 (5.3)	45 (4.7)	
Hysterectomy	43,438 (38.9)	8762 (44.4)	735 (43.4)	383 (40.2)	<0.001
Bilateral oophorectomy	19,766 (17.7)	4109 (20.8)	343 (20.2)	181 (19.0)	<0.001
Parity numbers					
0	13,609 (12.2)	2352 (11.9)	221 (13.0)	131 (13.8)	<0.001
1	9675 (8.7)	1699 (8.6)	157 (9.3)	88 (9.2)	
2	27,657 (24.8)	5084 (25.8)	448 (26.4)	247 (26.0)	
3	26,645 (23.9)	5031 (25.5)	383 (22.6)	239 (25.1)	
4	17,117 (15.3)	2970 (15.1)	235 (13.9)	116 (12.2)	
5	17,037 (15.3)	2599 (13.2)	251 (14.8)	131 (13.8)	
Age at menarche	12.62 (1.48)	12.48 (1.48)	12.70 (1.60)	12.59 (1.50)	<0.001
Age at menopause	48.3 (6.2)	47.8 (6.7)	47.6 (6.6)	48.1 (6.7)	<0.001
Family history of breast cancer	18,996 (17.0)	3587 (18.2)	298 (17.6)	161 (16.9)	<0.001
Mammogram ever	106,732 (95.5)	19,147 (97.0)	1629 (96.1)	928 (97.5)	<0.001
Benign breast disease	21,954 (19.7)	4500 (22.8)	405 (23.9)	210 (22.1)	<0.001
History of diabetes	4596 (4.1)	932 (4.7)	89 (5.3)	40 (4.2)	0.001
Duration of unopposed estrogen use					
Years (continuous)	3.18 (6.77)	4.88 (8.46)	4.07 (7.70)	4.34 (8.05)	<0.001
Time group					
None	74,496 (66.7)	11,372 (57.6)	1073 (63.3)	588 (61.8)	<0.001
<5 years	14,509 (13.0)	2630 (13.3)	204 (12.0)	110 (11.5)	
5+ years	22,732 (20.3)	5733 (29.1)	418 (24.7)	254 (26.7)	
Duration of estrogen+progestogen use					
Years (continuous)	1.53 (3.70)	1.89 (4.28)	1.62 (3.70)	1.94 (4.08)	<0.001
Time group					
None	82,101 (73.5)	13,921 (70.5)	1218 (71.9)	646 (67.9)	<0.001
<5 years	15,204 (13.6)	2797 (14.2)	234 (13.8)	151 (15.9)	
5+ years	14,432 (12.9)	3017 (15.3)	243 (14.3)	155 (16.2)	

(*continued*)

TABLE 1. (CONTINUED)

	Without history of thyroid disorder (n = 111,740)	*With history of hypothyroidism* (n = 19,735)	*With history of hyperthyroidism* (n = 1695)	*With history of mixed thyroid disorder* (n = 952)	p
Duration of any MHT use					
Years (continuous)	4.57 (7.10)	6.56 (8.55)	5.49 (7.80)	6.03 (8.14)	<0.001
Time group					
None	50,560 (45.3)	6934 (35.1)	708 (41.8)	353 (37.1)	<0.001
<5 years	25,248 (22.6)	4357 (22.1)	353 (20.8)	207 (21.7)	
5+ years	35,927 (32.1)	8444 (42.8)	634 (37.4)	392 (41.2)	
Outcomes					
Any breast cancer	8230 (7.4)	1475 (7.5)	142 (8.4)	75 (7.9)	0.258
Invasive breast cancer	6769 (6.1)	1190 (6.0)	114 (6.7)	64 (6.7)	0.509
In situ breast cancer	1461 (1.3)	285 (1.4)	28 (1.7)	11 (1.2)	0.156
ER-positive assay	6090 (5.5)	1095 (5.6)	89 (5.3)	61 (6.4)	0.793
PR-positive assay	5107 (4.6)	928 (4.7)	69 (4.1)	50 (5.3)	0.428
HER2/NEU-positive assay	751 (0.7)	137 (0.7)	20 (1.2)	7 (0.7)	0.041
Tumor grade					
Well differentiated	1871 (1.7)	327 (1.7)	31 (1.8)	21 (2.2)	0.270
Moderately differentiated	3331 (3.0)	574 (2.9)	47 (2.8)	28 (2.9)	
Poorly differentiated	1894 (1.7)	370 (1.9)	38 (2.2)	13 (1.4)	
Anaplastic	406 (0.4)	78 (0.4)	11 (0.7)	4 (0.4)	
Unknown	728 (0.7)	126 (0.6)	15 (0.9)	9 (1.0)	
Tumor stage					
Localized	5103 (4.6)	898 (4.6)	92 (5.4)	50 (5.3)	0.480
Regional	1563 (1.4)	280 (1.4)	20 (1.2)	14 (1.5)	
Distant	103 (0.1)	12 (0.1)	2 (0.1)	0 (0.0)	
Histology					
Ductal invasive plus lobular *in situ*	199 (0.2)	37 (0.2)	2 (0.1)	3 (0.3)	0.690
Ductal invasive plus lobular invasive	442 (0.4)	82 (0.4)	3 (0.2)	8 (0.8)	
Lobular invasive plus ductal *in situ*	118 (0.1)	21 (0.1)	2 (0.1)	1 (0.1)	
Invasive cancer, ductal, and lobular NOS	155 (0.1)	20 (0.1)	4 (0.2)	1 (0.1)	
Ductal *in situ* plus lobular *in situ*	71 (0.1)	16 (0.1)	0 (0.0)	1 (0.1)	

CT, Clinical Trial; ER, estrogen receptor; HER, human epidermal growth factor receptor 2; MHT, menopausal hormone therapy; NOS, not otherwise specified; OS, Observational Study; PR, progesterone receptor; T3, triiodothyronine; T4, thyroxine; WHI, Women's Health Initiative.

of a self-reported thyroid disorder. The statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Average ages at enrollment were 62.8–63.9 years in the four groups defined by thyroid disorders. Among the 19,735 women who reported having a history of hypothyroidism, 91.9% were Caucasian (not of Hispanic origin), compared with 76.8% among the 1695 women with a history of hyperthyroidism, and 85.4% among the 952 women who reported having a history of mixed thyroid disorder. The hypothyroidism group had the highest average BMI and the hyperthyroidism group had the lowest (28.8 vs. 26.9, respectively). Among those with hypothyroidism, there was no significant difference in BMI between those who received thyroid replacement and those who did not. More women had a history of breastfeeding in the hypothyroidism group. Compared with those who did not have a thyroid disorder, women with any thyroid history were more likely to be current or former smokers and have a history of bilateral oophorectomy, benign breast disease, and diabetes. Those with a history of either hypo- or hyperthyroidism were also more likely to have a family history of breast cancer (Table 1).

In multiple variable models, hyperthyroidism and mixed thyroid disease both showed a small increased risk of invasive breast cancer, but neither reached statistical significance [HR 1.11, 95% CI 0.91–1.35; HR 1.13, 95% CI 0.88–1.45; respectively]. Hypothyroidism, however, showed an inverse association with invasive breast cancer [HR 0.91, 95% CI 0.86–0.97]; we also found a borderline significant risk reduction when we looked at the use of thyroid replacement medication [HR 0.88, 95% CI 0.78–1.00]. When we separated thyroid replacement medications by type, we found that the use of levothyroxine was the only one inversely associated with the risk of breast cancer in the fully adjusted model [HR 0.89, 95% CI 0.82–0.96] (Table 2).

Table 2. Hazard Ratios of Hyperthyroidism/Hypothyroidism and Breast Cancer Risk in the Women's Health Initiative Cohorts

Invasive breast cancer (No. of cases = 8137)

	Total No.	*Cases*	*Model 1*[a] *HR [95% CI]*	*Model 2*[b] *HR [95% CI]*
History of hyperthyroidism	1695	114	1.12 [0.93–1.35]	1.11 [0.91–1.35]
History of hypothyroidism	19,735	1190	0.98 [0.92–1.04]	0.91 [0.86–0.97]
History of mixed thyroid disease	952	64	1.14 [0.89–1.46]	1.13 [0.88–1.45]
Use of thyroid replacement medications	12,437	715	0.89 [0.79–0.99]	0.88 [0.78–1.00]

Fully adjusted model using medication types instead of thyroid diagnoses

				Selected medication frequencies		
Effect	*Wald chi-square*	p	*HR [95% CI]*	*With history of hypothyroidism*	*With history of hyperthyroidism*	*With history of mixed thyroid disorder*
T3 hypothyroidism medication	0.169	0.68	0.75 [0.19–2.99]	46 (0.2)	0 (0.0)	1 (0.1)
T3/T4 hypothyroidism medication	0.635	0.43	0.88 [0.63–1.22]	655 (3.3)	0 (0.0)	26 (2.7)
T4 hypothyroidism medication	8.394	0.004	0.89 [0.82–0.96]	11,483 (58.2)	0 (0.0)	692 (72.7)
Hyperthyroidism medications	0.178	0.67	0.74 [0.19–2.97]	0 (0.0)	45 (2.7)	3 (0.3)

Fully adjusted model includes age, race/ethnicity, body mass index, smoking, alcohol intake, duration and type of MHT, history of bilateral oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, breastfeeding, and hysterectomy.

[a]Model 1 is adjusted for age.

[b]Model 2 is adjusted for variables in Model 1 and for race/ethnicity, body mass index, smoking, alcohol intake, history and type of MHT, history of oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, and breastfeeding.

CI, confidence interval; HR, hazard ratio.

Table 3. Hazard Ratios of Hyperthyroidism/Hypothyroidism and Breast Cancer Risk in the Women's Health Initiative Cohorts by Ethnicity

Invasive breast cancer (No. of cases = 8137)

	Total No.	*Cases*	*Model 1*[a] *HR [95% CI]*	*Model 2*[b] *HR [95% CI]*
Participants with history of hyperthyroidism				
White (not of Hispanic origin)	1302	92	1.11 [0.90–1.36]	1.12 [0.90–1.38]
Black or African American	255	15	1.37 [0.82–2.29]	1.06 [0.56–1.98]
Hispanic/Latino	42	2	1.31 [0.32–5.28]	1.36 [0.33–5.54]
Asian or Pacific Islander	63	2	0.72 [0.18–2.92]	0.71 [0.17–2.86]
Other	33	3	1.83 [0.58–5.80]	1.67 [0.40–6.96]
Participants with history of hypothyroidism				
White (not of Hispanic origin)	18,127	1107	0.95 [0.89–1.01]	0.89 [0.83–0.95]
Black or African American	643	32	1.15 [0.80–1.64]	1.13 [0.77–1.66]
Hispanic/Latino	442	23	1.55 [1.00–2.40]	1.50 [0.95–2.36]
Asian or Pacific Islander	261	16	1.40 [0.84–2.35]	1.35 [0.80–2.30]
Other	262	12	0.91 [0.50–1.68]	0.96 [0.51–1.80]

[a]Model 1 is adjusted for age, cohort type (OS, CT).

[b]Model 2 is adjusted for variables in Model 1 and for race/ethnicity, body mass index, smoking, alcohol intake, history and type of MHT, history of oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, breastfeeding, and breastfeeding duration.

We next sought to determine whether the risk of invasive breast cancer in women with thyroid disease varied among different races/ethnicities. No significant differences in results were found in the fully adjusted model (Table 3).

We further compared the characteristics and stages of invasive breast cancer by the type of thyroid disorder. There were no significant differences in the SEER stages, histologic types, morphologic grades, and receptor status (ER, PR, HER2) between women without a thyroid disorder and those with a history of hyperthyroidism or hypothyroidism (Table 4).

A stratified analysis to examine the effect modification of MHT types and lengths showed that women with a history of hypothyroidism who had taken thyroid medications and had never used MHT had a 20% reduced risk of invasive breast cancer [HR 0.80, 95% CI 0.69–0.93]. Among menopausal women with hypothyroidism who received thyroid replacement therapy, the risk reduction disappeared with the use of MHT for any duration [HR 0.93, 95% CI 0.78–1.09 for MHT <5 years; HR 0.93, 95% CI 0.83–1.03 for MHT ≥5 years]. Women with a history of hyperthyroidism who had taken unopposed estrogen for <5 years had a 62% increased risk of invasive breast cancer [HR 1.62, 95% CI 1.01–2.58]. No significant risk was found for those who had used MHT for 5 years or more (Table 5).

Table 4. Invasive Breast Cancer Characteristics and Stages by Thyroid Disorder

	No thyroid disorder (n = 111,740)		*Hyperthyroidism (n = 1695)*			*Hypothyroidism (n = 19,735)*		
	No. of cases	*Incidence*[a]	*No. of cases*	*Incidence*[a]	*Age-adjusted HR [95% CI]*	*No. of cases*	*Incidence*[a]	*Age-adjusted HR [95% CI]*
SEER stage[b]								
Localized	5103	31.68	92	38.61	1.03 [0.84–1.27]	898	31.57	1.01 [0.94–1.08]
Regional	1563	9.70	20	8.39	0.96 [0.61–1.49]	289	10.16	1.03 [0.91–1.18]
Distant	103	0.64	2	0.84	1.23 [0.29–5.25]	12	0.42	1.15 [0.61–2.15]
Histology[b]								
Ductal	199	1.24	2	0.84	0.59 [0.15–2.39]	37	1.30	0.99 [0.70–1.42]
Lobular	118	0.73	2	0.84	0.96 [0.23–3.94]	21	0.74	1.01 [0.63–1.63]
Ductal and lobular	442	2.74	3	1.26	0.86 [0.27–2.68]	82	2.88	1.03 [0.81–1.30]
Missing or unknown	155	0.96	4	1.68	1.23 [0.45–3.35]	20	0.70	1.16 [0.72–1.85]
Morphology, grade[b]								
Well differentiated	1761	10.93	28	11.75	1.06 [0.73–1.55]	316	11.11	1.03 [0.91–1.16]
Moderately differentiated	2858	17.74	40	16.79	1.03 [0.75–1.41]	498	17.51	1.08 [0.98–1.19]
Poorly differentiated	1500	9.31	33	13.85	0.96 [0.68–1.36]	283	9.95	0.96 [0.84–1.09]
Anaplastic	119	0.74	3	1.26	0.37 [0.12–1.22]	14	0.49	1.01 [0.58–1.76]
Missing or unknown	531	3.30	10	4.20	0.74 [0.40–1.39]	79	2.78	0.92 [0.72–1.16]
Receptor status[b]								
ER								
Positive	5448	33.82	80	33.57	1.01 [0.81–1.27]	977	34.35	1.04 [0.97–1.11]
Negative	930	5.77	27	11.33	0.89 [0.61–1.30]	151	5.31	0.93 [0.79–1.11]
Borderline	8	0.05	1	0.42	9.84 [0.31–309.45]	1	0.04	0.39 [0.04–4.22]
Unknown	271	1.68	5	2.10	0.81 [0.34–1.98]	47	1.65	1.16 [0.85–1.59]
PR								
Positive	4587	28.48	61	25.60	1.01 [0.78–1.30]	831	29.22	1.05 [0.97–1.13]
Negative	1694	10.52	45	18.88	0.96 [0.71–1.29]	284	9.98	0.96 [0.85–1.09]
Borderline	36	0.22	0	0.00	—	5	0.18	0.80 [0.30–2.10]
Unknown	335	2.08	7	2.94	0.95 [0.45–2.00]	55	1.93	1.10 [0.83–1.47]
HER2								
Positive	703	4.36	19	7.97	0.99 [0.62–1.56]	124	4.36	0.95 [0.79–1.15]
Negative	4477	27.79	71	29.80	1.02 [0.81–1.29]	776	27.28	1.03 [0.96–1.11]
Borderline	52	0.32	1	0.42	0.89 [0.12–6.55]	8	0.28	1.33 [0.54–3.30]
Unknown	437	2.71	6	2.52	0.92 [0.41–2.06]	85	2.99	0.97 [0.77–1.23]
Triple negative								
No	6291	39.05	96	40.29	1.03 [0.84–1.26]	1117	39.27	1.03 [0.97–1.10]
Yes	478	2.97	18	7.55	0.92 [0.57–1.47]	73	2.57	0.85 [0.66–1.08]

Mixed thyroid disorder excluded.
[a]Incidence per 10,000 person-years follow-up.
[b]Invasive breast cancer only.
SEER, Surveillance, Epidemiology, and End Results.

TABLE 5. EFFECT MODIFICATION OF MENOPAUSAL HORMONE THERAPY TYPE (STRATIFIED ANALYSIS)

Any MHT use duration

	N *(%)*	*No. of invasive breast cancer cases*	*Incidence*[a]	*No. of years used MHT*	*Age-adjusted HR [95% CI]*	*Fully adjusted HR [95% CI]*
Full model—all						
No thyroid dx	111,740	6769	41.68	4.57 (7.10)	Ref.	Ref.
Hyperthyroid dx	1695	114	47.26	5.49 (7.80)	1.11 [0.92–1.34]	1.12 [0.93–1.36]
Any hypothyroid dx with no medication	7815	501	43.77	5.81 (7.99)	1.05 [0.96–1.15]	0.97 [0.89–1.07]
Any hypothyroid dx with medications	12,872	753	40.47	6.98 (8.81)	0.95 [0.88–1.02]	0.89 [0.83–0.97]
Duration of any MHT use: none						
No thyroid dx	50,560	2746	38.66	0 (0)	Ref.	Ref.
Hyperthyroid dx	708	40	41.56	0 (0)	1.07 [0.78–1.47]	1.10 [0.79–1.54]
Any hypothyroid dx with no medication	2963	180	43.09	0 (0)	1.13 [0.97–1.32]	1.03 [0.88–1.21]
Any hypothyroid dx with medications	4324	204	33.50	0 (0)	0.87 [0.75–1.00]	0.80 [0.69–0.93]
Duration of MHT use: <5 years						
No thyroid dx	25,248	1502	39.44	1.93 (1.29)	Ref.	Ref.
Hyperthyroid dx	353	27	53.45	1.90 (1.27)	1.36 [0.93–2.00]	1.40 [0.96–2.051]
Any hypothyroid dx with no medication	1792	115	42.81	1.94 (1.27)	1.08 [0.89–1.31]	1.01 [0.83–1.23]
Any hypothyroid dx with medications	2772	156	38.07	1.98 (1.30)	0.96 [0.81–1.14]	0.93 [0.78–1.09]
Duration of MHT use: 5 years or more						
No thyroid dx	35,927	2521	47.32	12.86 (7.25)	Ref.	Ref.
Hyperthyroid dx	634	47	49.77	13.63 (7.39)	1.00 [0.74–1.35]	1.01 [0.75–1.37]
Any hypothyroid dx with no medication	3060	206	44.96	13.71 (7.62)	0.94 [0.81–1.08]	0.90 [0.78–1.05]
Any hypothyroid dx with medications	5776	393	46.69	14.61 (8.10)	0.95 [0.85–1.05]	0.93 [0.83–1.03]

Unopposed estrogen (E)

	N *(%)*	*No. of invasive breast cancer cases*	*Incidence*[b]	*No. of years used E*	*Age-adjusted HR [95% CI]*	*Fully adjusted HR [95% CI]*
Full model—all						
No thyroid dx	111,740	6769	41.68	3.18 (6.77)	Ref.	Ref.
Hyperthyroidism dx	1695	114	47.26	4.07 (7.70)	1.11 [0.92–1.34]	1.12 [0.93–1.36]
Any hypothyroidism dx with no meds	7815	501	43.77	4.18 (7.83)	1.05 [0.96–1.15]	0.97 [0.89–1.07]
Any hypothyroidism dx with meds	12,872	753	40.47	5.27 (8.77)	0.95 [0.88–1.03]	0.89 [0.83–0.97]
Duration of unopposed estrogen use: none						
No thyroid dx	74,496	4599	42.53	0 (0)	Ref.	Ref.
Hyperthyroidism dx	1073	69	45.44	0 (0)	1.04 [0.81–1.32]	1.05 [0.82–1.35]
Any hypothyroidism dx with no meds	4764	319	45.81	0 (0)	1.08 [0.97–1.22]	0.98 [0.87–1.11]
Any hypothyroidism dx with meds	7196	429	41.15	0 (0)	0.95 [0.86–1.05]	0.87 [0.78–0.96]
Duration of unopposed estrogen use: <5 years						
No thyroid dx	14,509	815	38.61	1.83 (1.26)	Ref.	Ref.
Hyperthyroidism dx	204	18	62.52	1.79 (1.27)	1.62 [1.01–2.58]	1.62 [1.01–2.58]
Any hypothyroidism dx with no meds	1058	60	38.86	1.79 (1.21)	1.01 [0.77–1.31]	0.94 [0.72–1.22]
Any hypothyroidism dx with meds	1682	95	39.41	1.92 (1.30)	0.99 [0.80–1.23]	0.93 [0.75–1.15]

(*continued*)

TABLE 5. (CONTINUED)

Unopposed estrogen (E)

	N *(%)*	*No. of invasive breast cancer cases*	*Incidence*[b]	*No. of years used E*	*Age-adjusted HR [95% CI]*	*Fully adjusted HR [95% CI]*
Duration of unopposed estrogen use: 5 years or more						
No thyroid dx	22,732	1355	40.87	14.47 (7.92)	Ref.	Ref.
Hyperthyroidism dx	418	27	44.57	15.64 (7.78)	1.06 [0.72–1.57]	1.07 [0.73–1.58]
Any hypothyroidism dx with no meds	1993	122	41.53	15.44 (8.24)	0.99 [0.82–1.20]	0.96 [0.79–1.16]
Any hypothyroidism dx with meds	3994	229	39.69	16.18 (8.58)	0.95 [0.83–1.10]	0.91 [0.79–1.05]

Estrogen+progestogen

	N *(%)*	*No. of invasive breast cancer cases*	*Incidence*[c]	*No. of years used E+P*	*Age-adjusted HR [95% CI]*	*Fully adjusted HR [95% CI]*
Full model—all						
No thyroid dx	111,740	6769	41.68	1.43 (3.70)	Ref.	Ref.
Hyperthyroid dx	1695	114	47.26	1.62 (3.70)	1.11 [0.92–1.34]	1.12 [0.93–1.36]
Any hypothyroid dx with no medication	7815	501	43.77	1.81 (4.06)	1.05 [0.96–1.15]	0.97 [0.89–1.07]
Any hypothyroid dx with medications	12,872	753	40.47	1.94 (4.39)	0.95 [0.88–1.03]	0.89 [0.83–0.97]
Duration of estrogen+progestogen use: none						
No thyroid dx	82,101	4476	38.39	0 (0)	Ref.	Ref.
Hyperthyroid dx	1218	69	40.84	0 (0)	1.07 [0.84–1.36]	1.09 [0.85–1.40]
Any hypothyroid dx with no medication	5525	330	41.75	0 (0)	1.09 [0.98–1.22]	1.01 [0.90–1.14]
Any hypothyroid dx with medications	9042	459	35.79	0 (0)	0.93 [0.84–1.02]	0.87 [0.79–0.96]
Duration of estrogen+progestogen use: <5 years						
No thyroid dx	15,204	1026	42.98	1.94 (1.28)	Ref.	Ref.
Hyperthyroid dx	234	22	63.56	1.93 (1.25)	1.41 [0.92–2.18]	1.51 [0.98–2.34]
Any hypothyroid dx with no medication	1126	80	45.41	1.99 (1.27)	1.03 [0.82–1.30]	0.98 [0.78–1.23]
Any hypothyroid dx with medications	1822	113	40.27	1.94 (1.27)	0.93 [0.76–1.13]	0.89 [0.73–1.09]
Duration of estrogen+progestogen use: 5 years or more						
No thyroid dx	14,432	1267	57.75	9.82 (4.72)	Ref.	Ref.
Hyperthyroid dx	243	23	61.12	9.45 (4.42)	0.99 [0.64–1.53]	0.98 [0.64–1.51]
Any hypothyroid dx with no medication	1164	91	51.13	10.21 (4.78)	0.88 [0.71–1.09]	0.85 [0.68–1.05]
Any hypothyroid dx with medications	2008	181	60.86	10.67 (5.38)	0.99 [0.84–1.16]	0.95 [0.81–1.12]

[a]Incidence per 10,000 person-years follow-up.
MHT use × thyroid group interaction $p = 0.346$.
Fully adjusted model includes age, race/ethnicity, body mass index, smoking, alcohol intake, duration of menopausal hormone replacement therapy, history of hysterectomy/oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, and breastfeeding.

[b]Incidence per 10,000 person-years follow-up.
Unopposed estrogen duration × thyroid group interaction $p = 0.747$.
Fully adjusted model includes age, race/ethnicity, body mass index, smoking, alcohol intake, duration of menopausal hormone replacement therapy, history of hysterectomy/oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, and breastfeeding.

[c]Incidence per 10,000 person-years follow-up.
E + P use × thyroid group interaction $p = 0.497$.
Fully adjusted model includes age, race/ethnicity, body mass index, smoking, alcohol intake, duration of menopausal hormone replacement therapy, history of hysterectomy/oophorectomy, parity history and numbers, age at menarche, age at menopause, family history of breast cancer, mammogram ever, and breastfeeding.

dx, diagnosis.

Discussion

Among a total of 134,122 postmenopausal women in the WHI, we found that women with hypothyroidism had a 9% lower risk of breast cancer than women who did not report a thyroid disorder. In this cohort, the risk reduction was most significant—20%—among those who received thyroid hormone replacement and had never used MHT. The use of levothyroxine was associated with an 11% lower risk of breast cancer. There was no significant difference in breast cancer risk across race/ethnicities by thyroid disease status and no statistically significant differences in breast cancer characteristics.

The association between thyroid hormone and cancers has been investigated in many *in vivo* and *in vitro* studies, as early as 1896 when Beaston published on using thyroid extract to treat metastatic breast cancer in the Lancet (4,9,19,25,26). Specific alterations of thyroid hormone receptors (TRs) have been found in many different types of cancers, including breast cancer, and there are associations between TR expression and oncogene regulation (4,5,27,28). Mammary and thyroid glands share some physiological similarities; for one, both thyroid follicular cells and mammary lactating cells utilize the sodium-iodine symporter to facilitate iodine uptake and storage (29–32). The alveolar mammary cells utilize lactoperoxidase to oxidize iodine while the thyroid gland uses thyroperoxidase via a similar mechanism (33). In addition, the activation of TRs in mammary glands may induce differentiation and lobular growth of breast tissues, an effect similar to that seen with estrogen (4,27).

In *in vitro* studies, high levels of thyroid hormones seem to possess estrogen-like effects, promoting breast cancer proliferation and angiogenesis (4–7,9). In addition, triiodothyronine (T3) was found to increase breast cancer cell proliferation in some breast cancer cell lines (6). Evidence from epidemiological studies on postmenopausal women suggests that an increased T3/E2 ratio may promote breast cancer development (14,34,35). T3 levels have also been shown to have a positive correlation with breast cancer tumor size and the risk of lymph node metastasis in population-based studies (36).

Although several hypotheses have been proposed to explain the association between hypothyroidism and breast cancer, no consensus has been reached. A hypothyroid state reduced the size and proliferation of malignant breast tumors and increased tumor necrosis *in vitro,* but the tumors exhibited a higher metastatic occurrence (17,37). It has been suggested that hypothyroidism leads to hypersensitization of mammary glandular epithelium to estrogen and prolactin secondary to abnormally low circulating thyroid hormone (38). It has also been hypothesized that there is a genetic predisposition for both hypothyroidism and breast cancer (14).

Clinical studies have found a protective association between hypothyroidism and breast cancer development; this may be due to the biological effect of T3 at the cellular level, the interaction of T3 with TRs, or modulation of the thyrotropin receptor (TSH-R) (39). The antioxidant property of iodine may also play a role, especially considering the capacity of breast tissue to transport and concentrate iodide (40,41). To date, there is still limited epidemiologic evidence for the link between thyroid replacement treatment and the risk of breast cancer.

In this study, we found an inverse association between hypothyroidism and invasive breast cancer development among postmenopausal women; the risk reduction was most significant in women who received thyroid replacement treatment (specifically, levothyroxine) and had never used MHT.

The mechanism by which levothyroxine use is associated with a reduced risk of breast cancer in women with hypothyroidism remains unclear. It may be due to the difference in thyroid hormone and TSH levels among those who took levothyroxine and those who either were not on levothyroxine despite being overtly hypothyroid, or those who had subclinical hypothyroidism and thus had residual thyroid gland function. Interestingly, this relationship was not seen with the use of other thyroid replacement treatments.

The diminished protective effect of hypothyroidism in women who used MHT is consistent with the results from previous WHI trial arm studies that looked at the effects of MHT on the development of invasive breast cancer. In those studies there was a significantly increased risk in the group who received estrogen (conjugated equine estrogens 0.625 mg) plus 2.5 mg medroxyprogesterone acetate (MPA) after adjusting for confounders [HR 1.96, 95% CI 1.17–3.27] (42,43).

Thyroid disorders were self-reported at enrollment and all prescribed medications were reconciled by trained staff. It is important to note, however, that we did not include CIS of the breast in our study. This is because the prognosis of CIS of the breast is very different from that of invasive breast cancer. Besides, we found no significant associations between different thyroid disorders and CIS of the breast.

The finding that women with a history of hyperthyroidism and unopposed estrogen use for <5 years had a statistically significant 62% increased risk of developing invasive breast cancer should be interpreted with caution due to small sample sizes and multiple comparisons. It is, however, in agreement with the case/control study by Weng *et al.* (19).

Limitations

In this study, we were unable to determine whether the duration and severity of hyper- or hypothyroidism or treatment compliance played a role in the development of invasive breast cancer. We were not able to adjust for the severity of hypothyroidism since the thyroid disorder diagnosis was self-reported. Because of this, we were unable to determine whether the inverse association with hypothyroidism was directly related to the use of levothyroxine or from hypothyroidism itself. In addition, the total number of participants in other ethnic groups was much smaller compared with the Caucasian group in this cohort, making it difficult to generalize the findings to other ethnicities. Finally, all of our results should be interpreted cautiously due to multiple comparisons and the potential for residual confounding.

Conclusions

Hypothyroidism was associated with a lower risk of breast cancer development, and the relationship was strongest among those who received thyroid hormone replacement and had never used MHT (estrogen or estrogen plus progestin). Further *in vitro* and clinical studies are needed to elucidate the relevant mechanisms and associations.

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