Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study

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Abstract

Objective: The association between thyroid disease and breast cancer risk remains unclear. We, therefore examined the association between hypothyroidism, hyperthyroidism and breast cancer risk.

Design: This was a population-based cohort study.

Methods: Using nationwide registries, we identified all women in Denmark with a first-time hospital diagnosis of hypothyroidism or hyperthyroidism, 1978–2013. We estimated the excess risk of breast cancer among patients with hypothyroidism or hyperthyroidism compared with the expected risk in the general population, using standardized incidence ratios (SIRs) as a measure of risk ratio. Breast cancer diagnoses in the first 12 months following diagnosis of thyroid disease were excluded from the calculations to avoid diagnostic work-up bias.

Results: We included 61 873 women diagnosed with hypothyroidism and 80 343 women diagnosed with hyperthyroidism. Median follow-up time was 4.9 years (interquartile range (IQR): 1.8–9.5 years) for hypothyroidism and 7.4 years (IQR: 3.1–13.5 years) for hyperthyroidism. Hyperthyroidism was associated with a slightly increased breast cancer risk compared with the general population (SIR: 1.11, 95% CI: 1.07–1.16), which persisted beyond 5 years of follow-up (SIR: 1.13, 95% CI: 1.08–1.19). In comparison, hypothyroidism was associated with a slightly lower risk of breast cancer (SIR: 0.94, 95% CI: 0.88–1.00). Stratification by cancer stage at diagnosis, estrogen receptor status, age, comorbidity, history of alcohol-related disease and clinical diagnoses of obesity produced little change in cancer risk.

Conclusions: We found an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in women with hypothyroidism indicating an association between thyroid function level and breast cancer risk.

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Introduction

Breast cancer is the most frequent cancer in females, with 458 337 new cases diagnosed in Europe in 2012 (1). Endogenous and exogenous sex hormones play an important role in the etiology of breast cancer (2). *In vitro*, high levels of thyroid hormones have estrogen-like effects (3, 4), promoting breast cancer cell proliferation (5, 6) and stimulating angiogenesis (7). Therefore, hyperthyroidism, characterized by increased levels of thyroid hormones, may potentially also increase breast cancer risk.

Epidemiological evidence concerning thyroid disorders and breast cancer risk remains unclear. Some

epidemiological studies have reported increased risks associated with hypothyroidism (8, 9), hyperthyroidism (10, 11, 12), goiter (13) and thyroid autoimmune diseases (14, 15), while others have found no association (9, 16, 17, 18). Only four studies employed a cohort design (9, 11, 12, 15); in case–control studies, reverse causation is a plausible competing explanation since breast cancer or its treatment may affect thyroid hormone levels (19). Moreover, some studies have not distinguished between hypothyroidism and hyperthyroidism, despite their contrasting hormonal profiles (13, 16, 17). We conducted a

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nationwide population-based cohort study in Denmark to examine the association between hypothyroidism, hyperthyroidism and risk of breast cancer.

Subject and methods

Study setting

In this nationwide population-based cohort study in Denmark we included data from 1 January 1978 to 31 November 2013. The Danish National Health Service guarantees tax-supported health care for all residents. Health service utilization is tracked by several nationwide registries, which are linkable using each resident's universal personal identifier, assigned to all Danish residents at birth or upon immigration since 1968 (20). Our study's source population consisted of the 4 177 429 women who resided in Denmark during the study period.

Hypothyroidism and hyperthyroidism

The Danish National Patient Registry (DNPR) contains information on all inpatient hospitalizations at Danish non-psychiatric hospitals since 1977 and outpatient and emergency department visits since 1995 (21, 22). Each hospital visit is recorded by physicians with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases*, 8th edition (ICD-8) until the end of 1993, and ICD-10 thereafter. We used the DNPR to identify all women with a first-time diagnosis of hypothyroidism or hyperthyroidism from 1978 through 2013 (see [Supplementary Table 1 for codes](#), see section on [supplementary data](#) given at the end of this article). Women with a diagnosis of hypothyroidism and hyperthyroidism on the same date ($n=481$) were excluded, and women with hyperthyroidism who subsequently developed hypothyroidism ($n=8185$) or *vice versa* ($n=1895$) were censored on the date of the new diagnosis.

Breast cancer

To identify incident breast cancer cases, the cohorts of women with a diagnosis of hypothyroidism or hyperthyroidism were linked to the Danish Cancer Registry (DCR), which records all incident cancers in Denmark since 1943, with mandatory reporting since 1987 (23). We excluded women with a breast cancer diagnosis prior to the diagnosis of hypothyroidism or hyperthyroidism. Through the DCR, we also obtained data on breast cancer

stage at diagnosis (classified according to Summary Staging as localized vs non-localized disease). We also performed a linkage to the Danish Pathology Registry (24) to retrieve data on estrogen receptor (ER) status at breast cancer diagnosis starting in 1997 (as pathology data became available in that year).

Comorbid diseases

We computed the Charlson Comorbidity Index (CCI) scores for each patient based on all available DNPR inpatient hospitalization records preceding the date of diagnosis of hypothyroidism or hyperthyroidism (25). We categorized severity of comorbidities as low (CCI score=0), medium (CCI score=1–2) or high (CCI score ≥ 3), excluding breast cancer diagnoses from the CCI score calculation. We also used the DNPR to access information on clinical diagnoses of obesity and alcohol-related disease (see [Supplementary Table 1 for codes](#)).

Statistical analysis

We followed women from the date of their first diagnosis of hypothyroidism or hyperthyroidism until incident breast cancer, death, emigration, or 31 November 2013, whichever came first. We computed the expected number of breast cancer cases using national incidence rates by age (5-year bands) and year of diagnosis (5-year periods) multiplied by person-years of follow-up. We computed standardized incidence ratios (SIRs) for breast cancer as the ratio of observed to expected cancers. Breast cancer diagnoses in the first 12 months following diagnosis of thyroid disease were excluded from the calculations to avoid overestimating the association by including prevalent occult breast cancers diagnosed during the diagnostic work-up for thyroid disease. Confidence intervals (CIs) for the SIRs were computed assuming that the observed number of cases in a specific category followed a Poisson distribution, using Byar's approximation (26). We stratified results by age at diagnosis, calendar period, CCI score categories, hospital diagnoses of obesity and alcohol-related disease, breast cancer stage at diagnosis and ER status (for women diagnosed between 1997 and 2013). We also computed the absolute risk of breast cancer with death as a competing risk. The follow-up period was categorized as 1–5 years and >5 years. As radioactive iodine (RAI) treatment may increase breast cancer risk (27), we conducted a sensitivity analysis in which follow-up was censored at initiation of RAI treatment. Smoking is an established risk factor for Graves' disease (28), we

therefore also conducted a sensitivity analysis excluding patients with Graves' disease in order to reduce potential confounding by smoking. We restricted this analysis to 1994–2011, the period during which there was a specific code for Graves' disease in the Danish ICD version (see [Supplementary Table 1 for codes](#)). Finally, we conducted a sensitivity analysis restricted to women who were diagnosed with hypothyroidism or hyperthyroidism starting in 1995 or later in order to capture information on outpatient diagnoses.

The study was approved by the Danish Data Protection Agency, record number 1-16-02-1-08. Studies based on registry data in Denmark do not require informed consent.

Results

There were 61 873 women diagnosed with hypothyroidism (median age at diagnosis: 71 years, interquartile range (IQR): 52–82 years) and 80 343 women diagnosed with hyperthyroidism (median age: 70 years, IQR: 55–82 years). Median follow-up was 4.9 years (IQR: 1.8–9.8 years) for patients with hypothyroidism and 7.4 years (IQR: 3.1–13.5 years) for patients with hyperthyroidism respectively. The proportion of women diagnosed with hypothyroidism increased substantially over time. In the calendar periods when outpatient diagnoses were available, 15.0% of hypothyroidism cases were diagnosed during 1998–2002, compared with 35.2% during 2008–2013 ([Table 1](#)). The corresponding percentages for hyperthyroidism were 20.4 and 20.6%. Most patients had no comorbidity requiring hospitalization at the time of diagnosis of hypothyroidism (65.8%) or hyperthyroidism (74.8%). Hospital diagnoses of obesity were more prevalent among women with hypothyroidism compared with hyperthyroidism (8.5 vs 3.5%). Less than 2% had a diagnosis of alcohol-related disease.

Overall, hyperthyroidism was associated with an increased risk of breast cancer (SIR: 1.11, 95% CI: 1.07–1.16), while hypothyroidism was associated with a slightly decreased risk of breast cancer (SIR: 0.94, 95% CI: 0.88–1.00) ([Table 2](#)). The hyperthyroidism-associated increased risk persisted beyond 5 years of follow-up (SIR: 1.13, 95% CI: 1.08–1.19). Stratification by cancer stage at diagnosis, ER status, age, comorbidity, history of alcohol-related disease and clinical diagnoses of obesity produced little change in breast cancer risk. Breast cancer risk in women with hyperthyroidism was unaffected by censoring at RAI treatment initiation (SIR: 1.08, 95% CI: 0.98–1.18, during 2002–2013) or by exclusion of patients with Graves' disease (SIR: 1.09, 95% CI: 1.02–1.16, during 1994–2011).

Table 1 Descriptive characteristics of women diagnosed with hypothyroidism or hyperthyroidism, Denmark, 1978–2013.

	Hypothyroidism		Hyperthyroidism	
	Number	%	Number	%
Total	61 873	100	80 343	100
Age at time of diagnosis				
<30 years	5594	9.0	6655	8.3
30–49 years	14 546	23.5	20 661	25.7
50–69 years	19 292	31.2	27 861	34.7
≥70 years	22 441	36.3	25 166	31.3
Calendar period at time of diagnosis				
1978–1982	3 175	5.1	6599	8.2
1983–1987	3403	5.5	5605	7.0
1988–1992	4431	7.2	6563	8.2
1993–1997	6346	10.3	12 634	15.7
1998–2002	9271	15.0	16 372	20.4
2003–2007	13 463	21.8	16 059	20.0
2008–2013	21 784	35.2	16 511	20.6
Charlson comorbidity index score				
Low (0)	40 729	65.8	60 081	74.8
Moderate (1–2)	16 577	26.8	16 687	20.8
High (≥3)	4567	7.4	3575	4.5
Obesity diagnosis				
No	56 754	91.7	77 512	96.5
Yes	5119	8.3	2831	3.5
Alcohol-related disease				
No	60 221	97.3	79 306	98.7
Yes	1652	2.7	1037	1.3

Between 1995 and 2013, 48 363 women had a diagnosis of hypothyroidism, of which 20 225 (41.8%) were inpatient diagnoses and 28 138 (58.2%) were outpatient diagnoses. Over the same period, 56 877 women had a diagnosis of hyperthyroidism. Of these women, 19 532 (34.3%) had inpatient diagnoses and 37 345 (65.7%) had outpatient diagnoses. Restricting the study period to 1995–2013 produced the same overall SIR estimates as the main analysis ([Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article). Stratification by inpatient vs outpatient diagnoses indicated a slightly higher breast cancer risk increase associated with outpatient diagnoses (SIR: 1.17, 95% CI: 1.06–1.29) of hyperthyroidism compared with inpatient diagnoses (SIR: 1.07, 95% CI: 0.94–1.22), particularly after 5 years of follow-up ([Supplementary Table 2](#)).

Discussion

This nationwide population-based cohort study spanning over a 30-year period revealed an elevated risk of breast cancer in women with hyperthyroidism, which increased with longer follow-up. Over the same period, women with

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Table 2 Standardized incidence ratios for breast cancer in women with hypothyroidism and hyperthyroidism, Denmark, 1978–2013.

	Women with hypothyroidism			Women with hyperthyroidism		
	No. of person-years	Observed/expected cancer	SIR (95% CI)	No. of person-years	Observed/expected cancer	SIR (95% CI)
Overall	36 1640	970/1031	0.94 (0.88–1.00)	674 236	2122/1903	1.11 (1.07–1.16)
Age at diagnosis of thyroid disease						
<30 years	37 559	17/15	1.17 (0.68–1.88)	72 244	35/45	0.78 (0.54–1.08)
30–49 years	102 422	197/206	0.96 (0.83–1.10)	229 087	626/510	1.23 (1.13–1.33)
50–69 years	137 188	486/505	0.96 (0.88–1.05)	255 053	1004/922	1.09 (1.02–1.16)
≥70 years	84 472	270/306	0.88 (0.78–0.99)	117 852	457/426	1.07 (0.98–1.18)
Calendar period of the diagnosis of thyroid disease						
1978–1982	35 984	95/95	1.00 (0.81–1.23)	111 722	309/288	1.07 (0.96–1.20)
1983–1987	3292	79/92	0.85 (0.68–1.06)	79 651	250/215	1.17 (1.03–1.32)
1988–1992	41 069	145/122	1.19 (1.00–1.40)	77 714	249/220	1.13 (0.99–1.28)
1993–1997	63 914	181/188	0.96 (0.83–1.11)	139 540	475/403	1.18 (1.08–1.29)
1998–2002	76 474	194/223	0.87 (0.75–1.00)	141 060	448/415	1.08 (0.98–1.18)
2003–2007	76 232	191/221	0.87 (0.75–1.00)	96 007	302/283	1.07 (0.95–1.19)
2008–2013	35 045	85/89	0.95 (0.76–1.18)	28 542	89/79	1.12 (0.90–1.38)
Charlson comorbidity index score						
Low (0)	273 988	706/746	0.95 (0.88–1.02)	57 3498	1734/1563	1.11 (1.06–1.16)
Moderate (1–2)	75 678	217/242	0.90 (0.78–1.02)	89 699	346/300	1.16 (1.04–1.28)
High (≥3)	11 974	47/42	1.12 (0.82–1.49)	11 038	42/40	1.04 (0.75–1.41)
Obesity diagnosis						
No	337 465	918/963	0.95 (0.89–1.02)	659 357	2075/1860	1.12 (1.07–1.16)
Yes	24 175	52/68	0.77 (0.57–1.01)	14 878	47/44	1.08 (0.79–1.43)
Alcohol-related disease						
No	354 797	943/1010	0.93 (0.88–1.00)	668 539	2106/1888	1.12 (1.07–1.16)
Yes	6842	27/21	1.30 (0.86–1.89)	5697	16/15	1.05 (0.60–1.71)
Breast cancer stage at diagnosis						
Localized	361 640	467/491	0.95 (0.87–1.04)	674 236	1012/909	1.11 (1.05–1.18)
Non-localized	361 640	377/427	0.88 (0.80–0.98)	674 236	883/809	1.09 (1.02–1.17)
Unknown stage	361 640	126/113	1.11 (0.93–1.32)	674 236	227/185	1.23 (1.07–1.40)
ER status ^a						
ER negative	200 431	67/77	0.87 (0.67–1.10)	293 504	124/118	1.05 (0.88–1.26)
ER positive	200 431	387/423	0.91 (0.83–1.01)	293 504	701/637	1.10 (1.02–1.19)
Missing ER status	200 431	55/70	0.78 (0.59–1.02)	293 504	100/103	0.97 (0.79–1.18)
Length of follow-up						
1–5 years	161 183	390/424	0.92 (0.83–1.02)	244 231	661/615	1.07 (0.99–1.16)
>5 years	200 457	580/607	0.96 (0.88–1.04)	430 005	1461/1288	1.13 (1.08–1.19)

^aPeriod for ER status: 1997–2013.

hypothyroidism experienced a slightly decreased risk of breast cancer.

During the last 50 years, several epidemiological studies have examined the association between thyroid disorders and the risk for breast cancer. Most of the previous studies examined the effect of thyroid hormone levels on breast cancer risk in a case–control setting (14, 16, 17, 29), in which reverse causation may be difficult to rule out. Our findings are in line with three of the earlier cohort studies that found an association between higher premorbid levels of thyroid hormone and breast cancer risk (11, 12, 15), while the fourth cohort study found an association between low levels of free thyroxine and an increased risk of breast cancer (9). The lack of increase in

the risk of breast cancer in women with hypothyroidism, observed in this study, is also in agreement with the results of a recent meta-analysis of 12 observational studies showing no association between hypothyroidism and breast cancer risk (18).

Several biological processes may underlie the observed associations between thyroid diseases and breast cancer risk. *In vitro* studies have demonstrated a proliferative effect of triiodothyronine (T₃, the active thyroid hormone) in the breast (5, 6). At the cellular level, T₃ binds to high-affinity nuclear receptors and induces transcription of target genes involved in energy homeostasis and cell proliferation. *In vitro* studies suggest a critical role of these receptors in breast cancer development (5, 30, 31).

In contrast to the experimental evidence that T_3 and estrogen synergistically stimulate certain breast cancer cell lines (3, 4, 6, 32), in our study, the association between hyperthyroidism and breast cancer risk was not modified by ER status.

We conducted a large nationwide population-based cohort study, with complete follow-up and highly valid data for thyroid disease (21, 23, 33) and breast cancer diagnoses (34, 35). The higher incidence of hyperthyroidism compared with hypothyroidism is in agreement with previous studies (36), as is the increased incidence of thyroid disease over time (37). One contributing factor to the higher incidence in hyperthyroidism is the fact that before 1995 only inpatient diagnosis were recorded in the DNPR (21), and hyperthyroidism is more likely than hypothyroidism to be diagnosed and treated in an inpatient setting as also shown in our study. However, a sensitivity analysis restricted to patients diagnosed from 1995 onward and stratified by inpatient vs outpatient diagnoses, yielded similar findings. A limitation of our study was the lack of laboratory data. We were therefore unable to distinguish between clinical and subclinical thyroid disease, as we were also unable to link the hormone levels at time of diagnosis to breast cancer risk. Of note, the exposure window in hyperthyroidism is short, as the hyperthyroid state is rapidly diagnosed, and ensuing treatment normalizes thyroid levels within a few weeks (38). Finally, the observed association between hyperthyroidism and breast cancer risk may have been underestimated due to incompletely ascertained (and therefore not adjusted for) lifestyle risk factors for breast cancer, such as obesity and alcohol consumption, both of which are associated with a reduced risk of hyperthyroidism (28, 39) but an increased risk of breast cancer (40). We stratified our analyses by hospital diagnoses of obesity and alcohol-related illness, however, these diagnoses are likely to capture only the most severe cases. Smoking has been associated with an increased risk of Graves' disease (28), but has no consistent association with breast cancer risk (41), and exclusion of patients with Graves' disease did not change our estimates. Finally, we did not address the role of hormonal treatment in the observed association. The role of treatment should be explored in further studies.

In conclusion, we found an increased risk of breast cancer in women with hyperthyroidism and a slightly decreased risk in women with hypothyroidism suggesting an association between the thyroid function level and breast cancer risk.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-0989>.

Declaration of interest

The authors report no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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