Prospective evaluation of circulating plasma thyroid hormones concentrations and breast cancer risk in the EPIC cohort

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Summary

Background **Hyperthyroidism has been associated with increased risk of breast cancer and *in vitro* studies have shown that thyroid hormones may influence breast tumorigenesis. We aimed to study associations between pre-diagnostic circulating thyroid hormone concentrations and breast cancer risk.**

Methods **We evaluated associations between breast cancer risk and circulating concentrations of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), fT3/fT4 ratio, and anti-thyroid peroxidase antibody (TPO-Ab) positivity, in plasma samples from 1518 invasive breast cancer cases (diagnosed between 2 and 14 years after blood collection) and 1518 matched controls from a case–control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort using validated immunoassays. Conditional logistic**

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regression models were used to evaluate associations with breast cancer, with adjustment for established breast cancer risk factors.

Findings In fully adjusted models, fT3 ($OR_{per\ standard\ deviation\ (SD)}$ (95% CI) = 1.16 (1.05–1.29)) and fT4 ($OR_{per\ SD}$ = 1.11 (1.01–1.22)) concentrations were positively associated with breast cancer risk. For fT3, the association was stronger for HER2-positive tumours (HER2+: $OR_{per\ SD}$ = 1.59 (1.20–2.11); HER2–: $OR_{per\ SD}$ = 1.10 (0.98–1.23)) compared to other tumour types (P-heterogeneity = 0.01). TSH concentrations, fT3/fT4 ratio, and TPO-Ab positivity were not associated with breast cancer risk.

Interpretation In this large-scale study, higher prediagnostic circulating fT3 and fT4 concentrations were associated with increased breast cancer risk, particularly for HER2-positive tumours. Confirming these findings is critical to achieving a better understanding of the associations between thyroid function and breast cancer risk, which may inform personalised prevention.

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Keywords: Breast cancer; Thyroid hormones; Thyroid-stimulating hormone; Prospective study

Research in context

Evidence before this study

A link between thyroid dysfunction and breast cancer has long been suspected, and could be mediated through thyroid hormones or auto-immune pathways. Previous prospective studies evaluating pre-diagnostic circulating thyroid hormone levels with breast cancer risk were conducted on limited sample sizes (around 800 cases), and few of them explored heterogeneity by breast cancer hormonal subtype.

Added value of this study

In a large (n = 1518 cases) nested case–control study, we investigated the association between circulating concentrations of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), the fT3/fT4 ratio, thyroid peroxidase antibodies (TPO-Ab) status, and breast cancer risk, overall and by breast cancer subtype. Concentrations of fT3 and fT4 were positively associated with breast cancer risk. For fT3, stronger associations were observed for HER2+ tumours. Concentrations of TSH, fT3/fT4 ratio, and TPO-Ab status were not associated with breast cancer risk overall or by tumour receptor status.

Implications of all the available evidence

Thyroid hormones may be involved in breast cancer development, and future studies should investigate breast cancer subtypes. Confirming these findings is critical to obtaining a better understanding of associations between thyroid function and breast cancer risk, which could open important perspectives for personalised prevention.

Introduction

Breast cancer is the second most common cancer worldwide, and affects mostly women, with almost 2.3 million new cases diagnosed in 2022.[1] Thyroid dysfunction also affects women much more frequently than men, with an estimated prevalence of 5–15% among women in iodine-replete populations.[2–4] A link between thyroid dysfunction and breast cancer has been long suspected–as early as 1896, Beatson started treating patients with inoperable breast cancer with thyroid extracts.[5] Over the last decades, several epidemiological studies have been undertaken to investigate a potential link between thyroid disorders and breast cancer,[4,6–10] yielding contrasting results, with evidence suggesting a higher risk of breast cancer among women with hyperthyroidism[4,7] and among women with auto-immune thyroid diseases.[7,9]

The major thyroid hormones triiodothyronine (T3) and thyroxine (T4) and their active forms, free T3 (fT3) and free T4 (fT4), may play an important role in breast cancer development.[11,12] In a meta-analysis of case–control studies, fT3 and fT4 concentrations were found to be higher in breast cancer cases compared with controls,[13] but these findings could have been influenced by reverse causality since hormones were measured after diagnosis. A limited number of prospective studies have evaluated pre-diagnostic thyroid hormone levels and breast cancer risk, with a maximum sample size of around 800 cases,[14–21] and few have explored heterogeneity by breast cancer hormonal subtype.[11,12]

Thyroid-stimulating hormone (TSH) is a polypeptide hormone secreted by the anterior pituitary gland that regulates thyroid function and thyroid hormone production.[22] Inverse associations have been

reported between measured TSH concentrations and breast cancer risk in some prospective studies[14,18,19] but not all,[15–17,20,21] which warrants further investigation.

It has also been hypothesised that hypothyroidism could influence breast cancer risk not only through a reduced production of thyroid hormones, but also through an autoimmune pathway.[23–25] Autoimmune thyroiditis, characterised by pathological levels of thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) sustained over years and a hypothyroid state, has been positively associated with breast cancer risk,[23,24] as have increased concentrations of TPO-Ab and Tg-Ab.[13] However, these associations have mainly been observed in studies on patients with breast cancer, who may have developed a general autoimmune response, and prospective studies are lacking.

Therefore, the present work aims to investigate the associations between circulating concentrations of TSH, fT3, fT4, fT3/fT4 ratio, TPO-Ab status, and breast cancer risk in a large case–control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), overall and by breast cancer subtypes.

Methods

Study population, blood collection and follow-up

EPIC is a prospective multi-centre cohort study including more than 500,000 participants recruited between 1992 and 2000 from ten European countries.[26] Female participants (n = 367,903) were aged 35–75 years old at inclusion. At recruitment, detailed information on dietary, lifestyle, reproductive and medical data was collected, and anthropometric variables were measured.[26] Blood was collected at baseline from around 70% of female participants according to a standardised protocol in France, Germany, Italy, the Netherlands, Norway, Spain and the United Kingdom.[26] Serum (except in Norway), plasma, erythrocytes and buffy coat aliquots were stored in liquid nitrogen (–196 °C) in a centralised biobank at the International Agency for Research on Cancer (IARC). In Denmark, blood fractions were stored in the vapour phase of liquid nitrogen containers (–150 °C) and in Sweden, they were stored at –80 °C in standard freezers.

Incident cancer cases were identified through record linkage with cancer registries in most countries, except for France and Germany, where cases were identified through health insurance records, cancer and pathology registries, and active follow-up of study participants. End of follow-up was defined as the latest date of complete follow-up for both cancer incidence and vital status (dates varied between centres, from June 2008 to December 2012).

Ethics

All participants provided written informed consent to participate in the EPIC study. The study was approved by the ethics committee of the IARC (No. 18-2) and all participating centres.

Selection of cases and controls

Participants for the current study were selected among women who had blood collected and were cancer-free (other than non-melanoma skin cancer) at recruitment into the cohort. Cancers were coded according to the Third Edition of the International Classification of Diseases for Oncology. All women diagnosed with first primary invasive breast cancer (code C50) at least two years after blood collection and before December 2012, for whom oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses of the tumours were available, were included as cases for the current study.

For each breast cancer case, one control was chosen at random from appropriate risk sets comprising all women who were alive and without a cancer diagnosis (other than non-melanoma skin cancer) at the time of diagnosis of the index case. Using incidence density sampling, controls were matched to cases on age (±6 months), centre of recruitment, menopausal status at blood collection (premenopausal, perimenopausal, postmenopausal, surgically postmenopausal[27]), use of exogenous sex steroid hormones at blood collection, time of day (±1 h), and fasting status at blood collection (non-fasting (<3 h since last meal), intermediate (3–6 h), fasting (>6 h), or unknown). Premenopausal women were also matched by phase of the menstrual cycle at blood collection.[27]

Of the 1521 case–control pairs available, two pairs were excluded because one member of the pair was pregnant at blood collection. An additional pair was excluded due to a technical issue with one sample, leading to a final analytical population of 1518 breast cancer cases and 1518 matched controls. This sample size provided 85% power to detect a relative risk of 1.24 between extreme quartiles of exposure.

Laboratory measurements

Plasma samples were analysed at IARC using validated immuno-assays to quantify TSH, fT3, fT4, and TPO-Ab.[28] Cases and their matched controls were analysed in the same analytical batch, and the laboratory technician performing the analysis was blinded to the case/control status of the samples.

Three quality control samples were included in duplicate in each batch of analyses. Overall, within-batch coefficients of variations (CVs) ranged from 4.5% for fT4 to 8.3% for fT3. Between-batch coefficients of variations ranged from 9.8% for fT4 to 20.0% for TPO-Ab. For each hormone, values below the lower limit of quantification were imputed to the lower limit of quantification of the assay (n = 97 for TSH; n = 1 for fT3; n = 39 for fT4) and values above the upper limit of quantification were imputed to this upper limit (n = 35

	Controls (n = 1518)	Cases (n = 1518)
Age at blood collection (years) (mean (SD))	52.5 (7.9)	52.5 (7.9)
Age at diagnosis (years) (mean (SD))		60.8 (8.3)
Time to diagnosis (years) (mean (SD))		8.6 (2.7)
ER status (%)		
Negative		296 (19.5)
Positive		1222 (80.5)
PR status (%)		
Negative		482 (31.8)
Positive		1036 (68.2)
HER2 status (%)		
Negative		1187 (78.2)
Positive		331 (21.8)
Fasting status at blood collection (%)		
No (<3 h since last meal)	731 (48.2)	730 (48.1)
In between (3–6 h since last meal)	272 (17.9)	273 (18.0)
Yes (>6 h since last meal)	515 (33.9)	515 (33.9)
Menopausal status at blood collection (%)		
Premenopausal	410 (27.0)	410 (27.0)
Postmenopausal (including surgical menopause)	816 (53.8)	816 (53.8)
Perimenopausal	292 (19.2)	292 (19.2)
Use of oral contraceptives or MHT at blood collection (%)	486 (32.0)	486 (32.0)
Age at first menstrual period (years) (mean (SD))	13.06 (1.57)	13.02 (1.53)
Number of full-term pregnancies (%)		
0	212 (14.0)	239 (15.7)
1	240 (15.8)	285 (18.8)
2	677 (44.6)	637 (42.0)
3 or more	389 (25.6)	357 (23.5)
Age at first full-term pregnancy[a] (years) (mean (SD))	24.9 (4.3)	25.3 (4.4)
Ever breastfed (%)		
Nulliparous	212 (14.0)	239 (15.7)
No	189 (12.5)	199 (13.1)
Yes	1117 (73.6)	1080 (71.1)
Education level (%)		
Primary/no schooling	589 (38.8)	575 (37.9)
Technical/professional/ secondary	627 (41.3)	629 (41.4)
Longer	302 (19.9)	314 (20.7)
Physical activity (Cambridge Index) (%)		
Inactive	306 (20.2)	337 (22.2)
Moderately inactive	616 (40.6)	570 (37.5)
Moderately active	325 (21.4)	336 (22.1)
Active	271 (17.9)	275 (18.1)
Smoking status (%)		
Never	865 (57.0)	861 (56.7)
Former	327 (21.5)	349 (23.0)
Current	326 (21.5)	308 (20.3)

(Table 1 continues on next page)

for TSH; none for fT4 and fT3). For TPO-Ab, values were dichotomised according to a cut-off recommended by the vendor (40 IU/mL), and samples showing TPO-Ab concentration above this threshold were considered TPO-Ab-positive. The cut-off of 40 IU/mL was chosen because varying the threshold from 30 to 60 IU/mL did not materially affect the proportion of positive individuals (11.3% with 40 IU/mL threshold; 12.7% for 30 IU/mL and 9.3% for 60 IU/mL).

Of note, samples from only 1212 case–control pairs were analysed for fT3 and fT4, since these analyses required samples not previously thawed, which were not available for the remaining participants. TSH and TPO-Ab measures are not affected by freeze/thaw cycles.

Statistics

Characteristics of selected cases and controls were described using mean and standard deviation (SD) or frequency and percentage. Hormone concentrations were described separately for cases and controls using geometric means and percentiles.

We analysed hormone concentrations as continuous variables and in quartiles derived using cut-offs identified among control participants, except for TPO-Ab which was categorised as positive vs negative according to the vendor's cut-off. We estimated the risk of breast cancer per SD increase in log-transformed hormone concentration (log-transformation reduced skewness), and by quartiles using the lowest quartile as the reference. We first used a conditional logistic regression model conditioned on matching variables to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We then evaluated a model additionally adjusted for established breast cancer risk factors at recruitment, including: age at menarche (continuous), number of full-term pregnancies (nulliparous/1/2/≥3), age at first full-term pregnancy (nulliparous/quartiles), breastfeeding (ever/never/nulliparous), use of oral contraceptives (ever/never), use of menopausal hormone therapy (ever/never/missing), smoking status (never/former/current), level of physical activity (Cambridge index[29]: inactive/moderately inactive/moderately active/active), alcohol consumption (non-drinker, 0–3 g/day, >3–12 g/day, >12–24 g/day, >24 g/day), education level (no schooling or primary/technical, professional or secondary/longer education), height (continuous), and body mass index (BMI) (continuous). For these variables, missing values were assigned the median (for continuous variables) or mode (for categorical variables) if they represented less than 5% of the population (as was the case for all continuous variables) otherwise, they were classified in a "missing" category (e.g. use of menopausal hormone therapy). For tests of linear trend across quartiles, participants were assigned the median concentration in each quartile and the

corresponding variables were modelled as a continuous term. Departure from linearity was evaluated using restricted cubic splines (N = 4 knots, at the 20th, 40th, 60th and 80th percentiles), compared with the main linear models on a continuous scale using likelihood ratio tests.

We also examined whether associations observed in the adjusted models differed by: menopausal status at blood collection (premenopausal/perimenopausal/postmenopausal (including surgical menopause)), use of sex steroid hormones (oral contraceptives or menopausal hormone therapy, yes/no) at blood collection, fasting status at blood collection (fasting (>6 h since last meal)/non-fasting (<3 h since last meal/in between (3–6 h since last meal)), or BMI at recruitment (</≥25 kg/m^2). For BMI, we used logistic regression adjusted for matching factors since BMI was not a matching variable and stratification would have resulted in exclusion of many case–control pairs. We also evaluated potential heterogeneity by breast cancer subtype using ER, PR, and HER2 status (positive/negative for each and combined as ER-PR-HER2–, ER-PR-HER2+, ER + PR ± HER2– (i.e. ER + HER2–, regardless of PR status); ER + PR ± HER2+ (i.e. ER + HER2+, regardless of PR status)), by age at diagnosis (</≥50 years), and by time from blood collection to diagnosis (</≥ 8.6 years (median)). Heterogeneity was tested using a likelihood ratio test after including an interaction term in the model.

As a sensitivity analysis, we evaluated associations between hormone concentrations and breast cancer risk after excluding participants with TPO-Ab positivity (resulting in 1348 cases and 1366 controls for TSH, 1073 cases and 1090 controls for fT3 and fT4), using logistic regression adjusted for matching criteria and the factors listed above. We also evaluated a fully adjusted model with mutual adjustment for fT3 and fT4 concentrations to account for potential correlations between these hormones.

To better understand potential associations between the measured hormones and breast cancer risk, we examined correlations between thyroid hormones and TSH among control participants, and for a subset of participants with available data from previous studies,[27,30–33] we also examined correlations with sex steroids (androstenedione, dehydroepiandrosterone-sulphate (DHEAS), oestrone, oestradiol, progesterone, testosterone), sex hormone binding globulin (SHBG), C-peptide, insulin-like growth factor 1 (IGF1), and IGF-binding protein 3 (IGFBP3). We first estimated residuals of each biomarker's concentration regressed on the analytical batches used for the measurements of the specific biomarkers. These residuals were then used to calculate partial Spearman's correlations separately in pre- and postmenopausal women, adjusted for age at blood collection, centre, and menstrual cycle phase at blood collection (for premenopausal women only).

All statistical tests were two-sided. Analyses were conducted using R version 4.2.1.

	Controls (n = 1518)	Cases (n = 1518)
(Continued from previous page)		
Alcohol consumption (g/day) (%)		
Non drinker	220 (14.5)	217 (14.3)
0–3	430 (28.3)	396 (26.1)
>3–12	447 (29.4)	428 (28.2)
>12–24	256 (16.9)	270 (17.8)
>24	165 (10.9)	207 (13.6)
Height (cm) (mean (SD))	161.5 (6.6)	162.1 (6.6)
BMI (kg/m^2) (mean (SD))	25.4 (4.1)	25.8 (4.7)
TPO-Ab Positive (%)	160 (10.5)	178 (11.7)

Abbreviations: BMI body mass index; ER oestrogen receptor; HER2 human epidermal growth factor receptor 2; PR progesterone receptor; SD standard deviation; TPO-Ab thyroid peroxidase antibodies. [a]Among parous women.

Table 1: **Population characteristics of study participants by case/control status.**

Role of funders

The funders were not involved in the design of the study; the collection, analysis or interpretation of the data; or the writing or submission of the manuscript for publication.

Results

Study population characteristics are described in Table 1. At blood collection, the average age was 52.5 years old, 33.9% of participants were fasting, 27.0% of participants were premenopausal, and 32.0% were using exogenous sex steroid hormones (oral contraceptives or menopausal hormone therapy). Cases were diagnosed on average 8.6 years after blood collection.

	N	Geometric mean (SD)	Median	5th percentile	25th percentile	75th percentile	95th percentile
Controls							
TSH (mIU/L)	1518	1.30 (2.36)	1.39	0.25	0.89	2.20	4.51
fT3 (pmol/L)	1203	6.08 (1.27)	6.13	4.15	5.38	7.01	8.47
fT4 (pmol/L)	1203	7.06 (1.36)	7.18	4.15	5.83	8.50	11.60
fT3/fT4	1203	0.86 (1.40)	0.86	0.50	0.70	1.06	1.47
Cases							
TSH (mIU/L)	1518	1.34 (2.31)	1.41	0.29	0.91	2.23	4.47
fT3 (pmol/L)	1203	6.23 (1.27)	6.31	4.18	5.44	7.15	8.75
fT4 (pmol/L)	1203	7.21 (1.36)	7.25	4.31	6.00	8.69	11.54
fT3/fT4	1203	0.86 (1.38)	0.86	0.52	0.71	1.04	1.46

Abbreviations: fT3 free triiodothyronine; fT4 free thyroxine; IU international unit; SD standard deviation; TSH thyroid-stimulating hormone.

Table 2: **Distribution of TSH, fT3 and fT4 plasma concentrations among cases and control participants.**

	Cases/controls	Base model[a]	Fully-adjusted model[b]
		OR (95% CI)	OR (95% CI)
TSH			
Per SD increment	1518/1518	1.04 (0.96–1.12)	1.02 (0.95–1.11)
Quartiles (mIU/L)			
≤0.89	362/380	1 (ref.)	1 (ref.)
(0.89, 1.39]	381/380	1.06 (0.86–1.30)	1.05 (0.85–1.30)
(1.39, 2.20]	388/378	1.08 (0.88–1.34)	1.06 (0.86–1.32)
>2.20	387/380	1.08 (0.87–1.35)	1.05 (0.84–1.32)
P-trend		*0.54*	*0.75*
fT3			
Per SD increment	1203/1203	1.17 (1.06–1.29)	1.16 (1.05–1.29)
Quartiles (pmol/L)			
≤5.38	282/301	1 (ref.)	1 (ref.)
(5.38, 6.13]	248/301	0.90 (0.70–1.15)	0.89 (0.69–1.15)
(6.13, 7.01]	328/300	1.26 (0.98–1.63)	1.23 (0.94–1.60)
>7.01	345/301	1.41 (1.07–1.85)	1.41 (1.06–1.87)
P-trend		*0.004*	*0.006*
fT4			
Per SD increment	1203/1203	1.09 (1.00–1.20)	1.11 (1.01–1.22)
Quartiles (pmol/L)			
≤5.83	271/301	1 (ref.)	1 (ref.)
(5.83, 7.18]	309/301	1.17 (0.92–1.49)	1.20 (0.94–1.53)
(7.18, 8.50]	287/300	1.10 (0.86–1.41)	1.17 (0.91–1.51)
>8.50	336/301	1.31 (1.02–1.70)	1.37 (1.05–1.79)
P-trend		*0.058*	*0.028*
fT3/fT4			
Per SD increment	1203/1203	1.02 (0.92–1.12)	0.99 (0.90–1.10)
Quartiles			
≤0.70	280/301	1 (ref.)	1 (ref.)
(0.70, 0.86]	324/301	1.17 (0.92–1.48)	1.19 (0.93–1.51)
(0.86, 1.06]	312/300	1.13 (0.88–1.45)	1.13 (0.87–1.46)
>1.06	287/301	1.03 (0.79–1.35)	0.97 (0.74–1.28)
P-trend		*0.92*	*0.53*
TPO-Ab			
Negative	1340/1358	1 (ref.)	1 (ref.)
Positive	178/160	1.12 (0.90–1.41)	1.11 (0.89–1.40)

Abbreviations: CI; confidence interval; fT3 free triiodothyronine; fT4 free thyroxine; OR odds ratio; Q quartile; SD standard deviation; TPO-Ab thyroid peroxidase antibodies; TSH thyroid-stimulating hormone. [a]Conditional logistic regression matched on centre of recruitment, age, menopausal status, phase of the menstrual cycle for premenopausal women, use of exogenous hormones at blood collection, time of the day and fasting status at blood collection. [b]Additionally adjusted for age at first menstrual period (numeric), number of full-term pregnancies (nulliparous/1/2/≥3), age at first full-term pregnancy (never pregnant/quartiles), breastfeeding (ever/never/nulliparous), use of oral contraceptives (ever/never), use of menopause hormonal treatment (ever/never/missing), smoking status (never/former/current), level of physical activity (inactive/moderately inactive/moderately active/active), alcohol consumption (non-drinker, 0–3 g/day, >3–12 g/day, >12–24 g/day, >24 g/day), education level (no schooling or primary/technical, professional or secondary/longer education), height (continuous), body mass index (continuous).

***Table 3*: Associations between TSH, fT3, fT4, and TPO-Ab status, and breast cancer risk overall.**

Overall, ER-positive, PR-positive, and HER2-positive tumours represented 80.5%, 68.2%, and 21.8% of cases respectively, with ER + PR ± HER2– representing 66.6%, ER + PR ± HER2+ 13.8%, ER-PR-HER2– 10.1%, and ER-PR-HER2+ 7.4% (not tabulated). Compared with controls, cases were more likely to be nulliparous (14.0% in controls; 15.7% in cases), and among alcohol consumers, were more likely to consume more than 24 g/day (10.9% in controls; 13.6% in cases).

The distributions of TSH, fT3, and fT4 concentrations in baseline blood samples are described for cases and controls in Table 2 and overall in Supplementary Figure S1 (Additional File 1).

As shown in Table 3, concentrations of fT3 were positively associated with breast cancer risk in both the base model ($OR_{per\ SD}$ (95% CI) = 1.17 (1.06–1.29); $OR_{quartile\ (Q)\ 4\ vs\ Q1}$ = 1.41 (1.07–1.85), P-trend across quartiles = 0.004) and the fully-adjusted model ($OR_{per\ SD}$ = 1.16 (1.05–1.29); $OR_{Q4\ vs\ Q1}$ = 1.41 (1.06–1.87), P-trend = 0.006). A positive association was also observed for fT4 (base model: $OR_{per\ SD}$ = 1.09 (1.00–1.20); $OR_{Q4\ vs\ Q1}$ = 1.31 (1.02–1.70), P-trend = 0.058; fully-adjusted model ($OR_{per\ SD}$ = 1.11 (1.01–1.22); $OR_{Q4\ vs\ Q1}$ = 1.37 (1.05–1.79), P-trend = 0.028)). TSH, fT3/fT4 ratio, and TPO-Ab positivity were not associated with breast cancer risk. There was no evidence of departure from linearity based on tests comparing models with hormone concentrations as continuous variables (per SD) and models including a restricted cubic spline (P-values, fully adjusted model: TSH = 0.82; fT3 = 0.47; fT4 = 0.91; fT3/fT4 = 0.19). When fT3 and fT4 concentrations were mutually adjusted for, the association between fT3 and breast cancer risk remained statistically significant ($OR_{per\ SD}$ = 1.14 (1.02–1.27), not tabulated), whereas the association with fT4 was attenuated and no longer statistically significant ($OR_{per\ SD}$ = 1.07 (0.97–1.18), not tabulated).

In subgroup analyses (Fig. 1), there was evidence for heterogeneity in the associations of fT3 with breast cancer risk by HER2 status (P-heterogeneity = 0.01; HER2–: $OR_{per\ SD}$ = 1.10 (0.98–1.23); HER2+: $OR_{per\ SD}$ = 1.59 (1.20–2.11)). When considering ER, PR, and HER2 combined, the strongest OR was observed for ER + PR ± HER2+ tumours ($OR_{per\ SD}$ = 1.76 (1.23–2.50); P-heterogeneity = 0.11). The association between fT3 and breast cancer risk was limited to women not using exogenous hormones (non-users: $OR_{per\ SD}$ = 1.24 (1.09–1.41); users: $OR_{per\ SD}$ = 1.03 (0.85–1.25); P-heterogeneity = 0.09), and to women diagnosed more than 8.6 years after blood collection (<8.6 years: $OR_{per\ SD}$ = 1.05 (0.90–1.23); ≥8.6 years: $OR_{per\ SD}$ = 1.26 (1.09–1.47); P-heterogeneity = 0.08). For TSH (Additional File 1; Supplementary Figure S2), we observed a suggestion of heterogeneity by hormone use at blood collection (P-heterogeneity = 0.06), with a non-significant positive association in non-users (non-users: $OR_{per\ SD}$ = 1.08 (0.98–1.19); users: $OR_{per\ SD}$ = 0.92 (0.80–1.06)). For fT4 (Fig. 2) and TPO-Ab (Additional File 1; Supplementary Figure S3), there was no evidence of heterogeneity for any of the associations examined (all P-heterogeneity ≥0.16 for fT4; ≥0.13 for TPO-Ab). Excluding TPO-Ab-positive participants did not modify the positive association between fT3 and breast cancer risk, while the association between fT4 and breast cancer risk was no longer statistically significant in TPO-Ab-negative participants (continuously

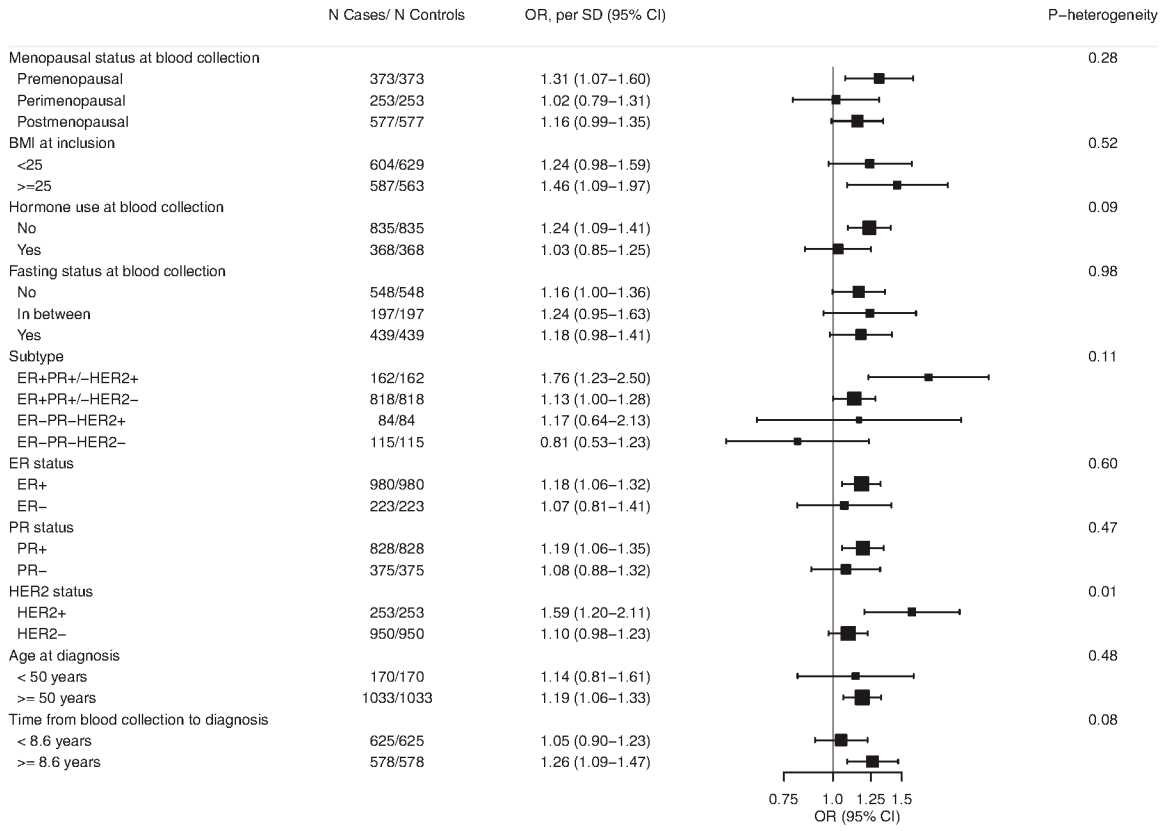

***Fig. 1:* Associations between fT3 and breast cancer risk in subgroups**. Odds ratios were obtained from logistic regression conditioned on matching variables (see main text), and adjusted for age at first menstrual period, number of full-term pregnancies, age at first full-term pregnancy, breastfeeding, use of oral contraceptives, use of menopause hormonal treatment, smoking status, level of physical activity, alcohol consumption, education level, height, body mass index. Abbreviations: BMI body mass index; ER oestrogen receptor; HER2 human epidermal growth factor receptor 2; CI; confidence interval; fT3 free triiodothyronine; OR odds ratio; PR progesterone receptor; SD standard deviation.

and in quartiles, Additional File 1; Supplementary Table S1).

In premenopausal and postmenopausal women, fT4 was positively correlated with fT3 (premenopausal = 0.19, post-menopausal = 0.27) and inversely correlated with TSH (r = –0.22 in pre- and postmenopausal women) and androstenedione (D4) concentrations (premenopausal = –0.37; postmenopausal = –0.34) (Fig. 3). TSH concentration was positively correlated with oestrone in premenopausal women (r = 0.41) and with androstenedione in postmenopausal women (r = 0.37) and inversely correlated with SHBG (r = –0.23), and IGF1 (r = –0.24) in postmenopausal women.

Discussion

In this large-scale prospective analysis of the association between circulating thyroid hormones and breast cancer risk, concentrations of fT3 and fT4 were positively associated with breast cancer risk. For fT3, stronger associations were observed for HER2+ tumours. Concentrations of TSH, fT3/fT4 ratio, and TPO-Ab status were not associated with breast cancer risk overall or by tumour receptor status.

Few prospective studies have been conducted on the association between circulating thyroid hormones and breast cancer risk.[14–21] The observed positive association for fT3 is in line with the results from the Malmö Preventive Project (n = 173 cases),[20] but contrasts with the absence of association reported overall for fT3 in the Malmö Diet and Cancer Study (n = 676 cases),[14,21] and in a large cohort of Korean women (n = 834 cases).[18]

Consistent with our findings, positive associations between fT4 and breast cancer risk have previously been reported in the Rotterdam Study (n = 227 cases),[17] the Malmö Diet and Cancer Study (n = 676 cases),[14,21] and the Kangbuk Samsung Health Study in Korean women (n = 834 cases).[18] A fourth prospective study based on Australian participants (38% premenopausal), suggested a positive association with fT4 of borderline significance (OR per unit increase = 1.07 (0.99–1.17)),

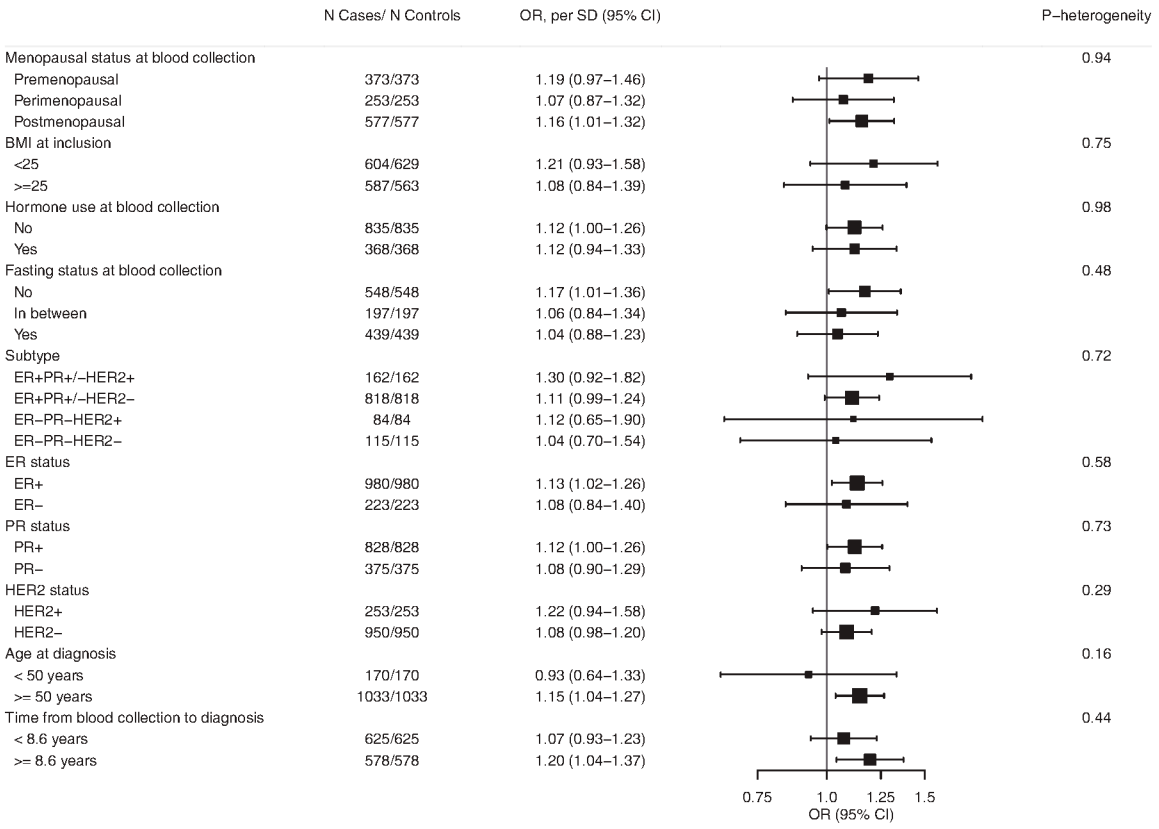

***Fig. 2:* Associations between fT4 and breast cancer risk in subgroups.** Odds ratios were obtained from logistic regression conditioned on matching variables (see main text), and adjusted for age at first menstrual period, number of full-term pregnancies, age at first full-term pregnancy, breastfeeding, use of oral contraceptives, use of menopause hormonal treatment, smoking status, level of physical activity, alcohol consumption, education level, height, body mass index. Abbreviations: BMI body mass index; ER oestrogen receptor; HER2 human epidermal growth factor receptor 2; CI; confidence interval; fT4 free thyroxine; OR odds ratio; PR progesterone receptor; SD standard deviation.

but included a more limited number of cases (n = 100).[15] Although one prospective study (n = 61 cases) reported higher breast cancer risk among postmenopausal women with low fT4 concentrations,[19] a recent, large Mendelian Randomisation analysis combining two large studies–the Breast Cancer Association Consortium (n = 122,977 cases) and the UK Biobank (n = 13,666 cases)–confirmed that genetically-predicted fT4 concentrations were positively associated with breast cancer risk).[34]

Although heterogeneity by ER or PR status was not statistically significant in the present work, our findings support stronger associations of thyroid hormones with breast cancer risk in hormone-receptor positive tumours, as previously suggested for fT4 in the Malmö Diet and Cancer Study and the Breast Cancer Association Consortium.[14,34] However, in our study, these stronger associations were seen mainly for fT3, in contrast with previous findings that fT3 was positively associated with breast cancer risk only for ER-tumours (but not ER+) in the Malmö Preventive Project,[35] and was not associated with ER + or ER-breast cancers in the Malmö Diet and Cancer Study.[14] Of note, in the present study, no strong (>0.50) correlations were observed between fT3 or fT4 and various hormones or binding proteins known to be associated with breast cancer risk. Evidence from experimental studies suggests a role for thyroid hormones in oestrogen-dependent proliferation of breast cancer cells through increased expression of oestrogen receptors, and the ability of thyroid hormone nuclear receptors to act as transcription factors on oestrogen receptor response elements in addition to thyroid response elements, since they share an identical half-site.[11] Thyroid hormones also act through membrane $\alpha v\beta 3$ integrin, which could activate phosphorylation of nuclear ERα.[11] Additional mechanisms may also promote tumour cell growth independently of ER, through the $\alpha v\beta 3$ integrin.[11,36,37] Furthermore, thyroid hormone receptors α and β have been observed in both malignant and

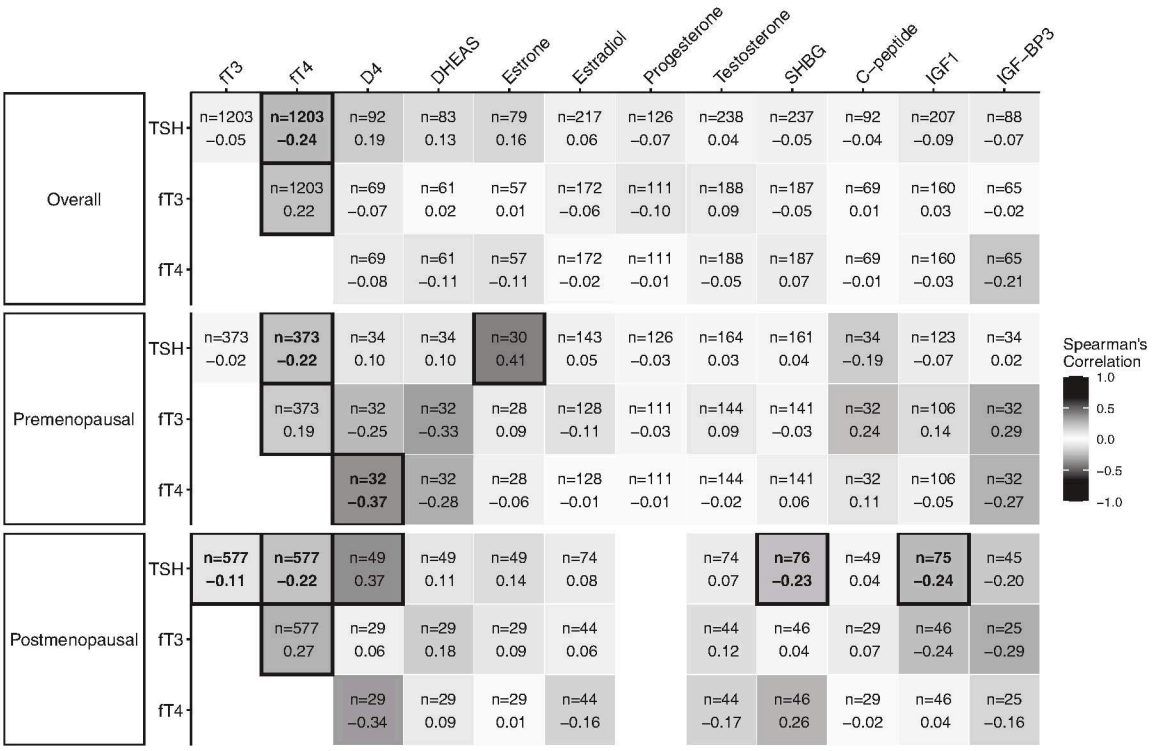

Fig. 3: **Correlations between circulating concentrations of thyroid hormones, sex steroids, C-peptide, IGF1 and IGF-BP among control participants**. Spearman's correlations were estimated between residuals of biomarker concentration regressed on analytical batch for the specific biomarker analysis. Partial correlations adjusted for age and centre at blood collection are presented here. For premenopausal women, phase of the menstrual cycle at blood collection was also adjusted for. Bold edges indicate statistically significant correlations ($P < 0.05$). Sample size used for each correlation is specified, and Spearman's correlation coefficient is shown for all. Abbreviations: D4 Androstenedione; DHEAS dehydroepiandrosterone sulphate; fT3 free triiodothyronine; fT4 free thyroxine; IGF1 insulin-like growth factor 1; IGF-BP3; IGF binding protein 3; SHBG sex hormone binding globulin.

normal breast cells, and substantial changes in the expression profile of these receptors may trigger breast cancer development.[38] Evidence regarding potential mechanisms of action on HER2+ tumours is limited, but a study in mice suggested that integrins could promote ERBB2 signalling in undifferentiated thyroid carcinoma, although not specific to the αvβ3 integrin.[39] Only one epidemiological study has previously investigated potential heterogeneity by HER2 status, using a retrospective cohort design, in which the ER + PR + HER2/neu-subtype was associated with higher pre-diagnosis TSH concentrations than the ER + PR + HER2/neu + subtype, but fT3 and fT4 were not studied.[40] Therefore, further investigation of HER2 status in prospective studies of thyroid hormones and breast cancer is warranted to clarify these associations, particularly for hormone receptor-positive and HER2+ tumours, which represent about 10% of breast cancer cases.[41]

We did not observe an association between breast cancer risk and the fT3/fT4 ratio, which reflects variability in the metabolism of thyroid hormones via the conversion of fT4 to fT3 through the action of deiodinases.[42] Although associations have been reported between the fT3/fT4 ratio and the prognosis of specific cardiometabolic diseases,[42] no prospective studies have evaluated its association with breast cancer risk.

Most prospective studies examining blood concentrations of TSH have not found an association with breast cancer overall.[14–17,20,21] An inverse association was observed among Korean women[18] and in a small Dutch study including only postmenopausal women (n = 61 cases),[19] as well as in the Malmö Diet and Cancer Study for ER + tumours only.[14] This finding was confirmed by a recent Mendelian Randomisation analysis using GWAS summary statistics from the Breast Cancer Association Consortium and the UK Biobank, showing a negative association between genetically predicted TSH and breast cancer risk, restricted to ER + tumours.[34] While we did not observe any association between TSH and breast cancer overall, there was a suggestion of heterogeneity by hormone use (menopausal hormone therapy or oral contraceptives) with a suggestive positive association restricted to non-users—a direction

that contrasts with previously reported associations. This positive association between TSH and breast cancer in women not using hormones aligns with the observed positive correlations between TSH and oestrone in premenopausal women, and androstenedione in postmenopausal women in our study. Although most studies adjusted for menopausal hormone therapy use, further analyses exploring potential effect modification by use of exogenous sex steroid hormones are needed, since cross-talk exists between sex steroids and thyroid hormones,[43] and increased breast cancer risk in hormone users may dilute or mask associations.[44]

In the present study, TPO-Ab positivity was not associated with breast cancer risk, consistent with findings from prospective studies in Australia and in the Netherlands.[15,19] In the Malmö Diet and Cancer Study, TPO-Ab positivity was not associated with overall breast cancer risk, but a lower risk was reported with increasing TPO-Ab concentrations,[21] limited to ER + or PR + tumours.[14] The positive association between fT3 and breast cancer risk identified in our study persisted even after exclusion of women with TPO-Ab positivity. Potential auto-immune mechanisms could support an association between hypothyroidism and lower breast cancer risk.[11] For instance, antibodies against natrium-iodide symporter–which facilitates iodide uptake and whose increased expression has been observed in breast cancer tissues[25]–are commonly found in autoimmune thyroid disease. However, our results point more towards a role of thyroid hormones rather than TPO-Ab.

Major strengths of this study include its large sample size, availability of hormone receptor and HER2 status information, and detailed data on lifestyle and anthropometric factors. In addition, the exclusion of cases diagnosed within two years after blood collection and the observation of stronger associations in cases diagnosed more than eight years after blood collection help rule out potential reverse causality. We were also able to examine correlations between thyroid hormones and other biomarkers previously measured in a subset of the population, showing no strong correlations, which provides interesting perspectives for the interpretation of these associations.

One of the main limitations of this study was the lack of clinical information about thyroid diseases or medications that could influence thyroid function. Moreover, biomarker concentrations were assessed at a single time point; however, TSH concentrations have been shown to remain stable over one to three years.[45] In addition, TSH and thyroid hormones are very stable when stored at –80 °C or below, and all EPIC samples are stored under these conditions. For fT3 and fT4, only previously unthawed samples were used. To better understand the associations studied here, prospective studies with repeated assessments of plasma thyroid hormone concentrations and detailed records of thyroid disease and medication use would be highly valuable. Lastly, since this study was conducted in a European population, findings may not be generalisable to other settings.

In this large prospective study investigating associations between plasma thyroid hormone concentrations and breast cancer, higher circulating fT3 and fT4 concentrations were associated with increased breast cancer risk, especially in HER2-positive tumours. Confirming these findings is critical to provide a better understanding of associations between thyroid function and breast cancer risk, which could open important perspectives for personalised prevention.

Contributors

The authors' responsibilities were as follows: SR conceived and designed the research; ASN analysed blood samples; MH analysed the data with assistance of CB and SR; MH and CB have accessed and verified the data; SR, MH, AF, TT, AG, ASN, CB, PF, and MJG were responsible for drafting the manuscript; AT, RK, RTF, MBS, GM, SS, RT, AC, ITG, KSO, CCE, MG, AAA, MDC, STT, AH, SC, and EKA provided the original data, information on the respective populations, and advice on the study design, analysis, and interpretation of the findings; all authors provided critical interpretation of the results and review of the first draft; all authors read and approved the final manuscript.

Data sharing statement

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of the International Agency for Research on Cancer (IARC), WHO, and the EPIC centres. The primary responsibility for accessing the data, obtained in the frame of the present publication, belongs to the EPIC centres that provided them. Access to EPIC data can be requested to the EPIC Steering Committee, as detailed in the EPIC-Europe Access Policy.

Declaration of interests

EKA consults for Servier Pharmaceuticals. STT received a research fellowship from the Health Research Council of New Zealand and a project grant from the Auckland Medical Research Foundation. All other authors declare no conflicts of interest.

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Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.106011.

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