CLINICAL STUDY

Triiodothyronine levels in relation to mortality from breast cancer and all causes: a population-based prospective cohort study

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Abstract

Objective: The potential association between thyroid hormones and breast cancer has been investigated in a large number of studies without conclusive results. This study investigated triiodothyronine (T₃) levels in relation to breast cancer mortality in a population with no breast cancer patients at baseline. An additional aim was to study T₃ levels in relation to mortality from other cancers and all-cause mortality.

Design and methods: This was a population-based prospective cohort study including 2185 women in whom T₃ levels were measured as part of a preventive health project, i.e. before diagnosis in women who later developed breast cancer. Mean follow-up was 24.1 years and record-linkage to The Swedish Cause-of-Death registry identified 471 women who died: 26 out of breast cancer and 182 from other cancers. Mortality was assessed using a Cox's analysis, yielding hazard ratios (HRs), with 95% confidence intervals. Analyses of T₃ as a continuous variable were repeated for pre- and peri/postmenopausal women separately.

Results: T₃ levels were positively associated with the risk of breast cancer-specific death in the age-adjusted analysis: HR for T₃ as a continuous variable was 2.80 (1.26–6.25). However, the crude analysis did not reach statistical significance. Breast cancer mortality was even higher in postmenopausal women: 3.73 (1.69–8.22), but stratified analyses included few events. There were no statistically significant associations between T₃ levels and deaths from other cancers, age-adjusted HR: 1.09 (0.72–1.65) or all-cause mortality (1.25:0.97–1.60).

Conclusions: This study, the first of its kind on prospectively measured T₃ levels, indicates that T₃ levels are positively associated with breast cancer-specific mortality and that this is not related to a general effect on all-cause mortality.

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Introduction

Thyroid disorders are common in women and an association with breast cancer would have a large impact. A large number of cross-sectional studies have investigated the association between breast cancer and thyroid disease, or levels of thyroid hormones, but these studies have been inconclusive (1, 2, 3). Two recent prospective studies have, however, found a positive association between pre-diagnostic thyroid hormone levels and breast cancer risk (4, 5). These studies did not find any corresponding association between TSH and risk (ibid).

In spite of the potentially large clinical relevance, there are only two small studies, including 84 and 47 patients respectively, on thyroid hormones and clinical outcome, i.e. survival following breast cancer, but they found no clear associations (6, 7). A problem in studies

measuring thyroid hormones in breast cancer patients is, however, that the disease *per se*, surgery, or adjuvant treatment may affect hormonal levels.

In order to investigate whether there is a clinically important association between thyroid hormone levels and breast cancer, the most relevant measurement is probably the breast cancer-specific mortality in a population with no breast cancer at baseline; this would reflect the net result of incidence and survival in a population. The only previous study on thyroid conditions and breast cancer mortality to our knowledge is Goldman *et al.* (8), but they found no association. They did, however, not include information on thyroid hormonal levels.

This study is a population-based, prospective cohort study including 2185 women with no breast cancer at baseline and in whom triiodothyronine (T₃) levels were measured as part of a preventive health project,

i.e. before diagnosis in women who developed breast cancer. In a previous study based on this cohort, we have found a positive association between T_3 levels and the risk of breast cancer (4), but it is not known whether this leads to a corresponding increase in breast cancer mortality.

The aim of this study was to investigate serum levels of T_3 in relation to breast cancer mortality in a population with no breast cancer patients at baseline. An additional aim was to study T_3 levels in relation to all-cause mortality.

Materials and methods

The Malmö Preventive Project

Originally, 10 902 women participated in the Malmö Preventive Project. The project was established in 1974 when residents in Malmö, a city in southern Sweden, were invited to participate in a health survey. Entire birth cohorts, men and women, were examined until 1992 when the department closed. Approximately 70% of invited subjects participated (9).

All women answered a questionnaire concerning sociodemographic information, lifestyle habits, and medical history. Questions on reproductive factors, e.g. menopausal status, were only included in women screened from April 1983 and onward. BMI (kg/m^2) was assessed at baseline examination (9). A subject was considered to have a history of goiter if the question 'have you been treated for goiter' was answered with 'yes'. There was no available information on specific type of previous thyroid disorders or type of treatment. The study was approved by the ethics committee at Lund University: Dnr 652/2005 and Dnr 501/2006.

T_3 analysis

Blood samples were taken after an overnight fast with the patient in the supine position. The serum samples were analyzed for T_3 and TSH in women born in 1928 and 1941 and examined in 1983 and 1984. In women born in 1935 (examined from 1990 to 1992), T_3 was only measured in a subset of all women, i.e. those with pathological TSH values, a history of thyroid disease, or those with an enlarged thyroid gland at examination. In addition to this, the attending physician could also decide to analyze T_3 (4). No analysis of thyroxine (T_4) had been performed at baseline in these women. T_3 was measured by a double antibody RIA (reference interval 0.9–3.2 mmol/l) (10). Only six women had a value above the upper reference limit.

Study cohort and follow-up on mortality

Among 10 902 women, reproductive data including menopausal status had been assessed in 8051 subjects.

T_3 had been measured in 2383 women (1161 born in 1928, 907 born in 1941, and 315 born in 1935). Women with prevalent breast cancer ($n=35$), goiter ($n=167$), or both ($n=4$) were identified and excluded from the study. Finally, the study population consisted of 2185 women with information on T_3 and without breast cancer at baseline or a record of goiter. Information on vital status and cause of death was retrieved from the Swedish Cause-of-Death Registry up until 31 December 2010.

Statistical analysis

Quartile cut-points for T_3 were based on the distribution among all women in the study population. T_3 levels were investigated in relation to factors known to be associated with subsequent mortality, i.e. age at baseline, educational levels, alcohol consumption, and BMI. A Kendall's τ -b test was used giving correlation coefficients (τ_b) and corresponding P values. Smoking was compared in relation to T_3 quartiles using a χ^2 test. A Bonferroni's correction was performed for P values in pairwise χ^2 comparisons multiplying the P value with the number of comparisons. A two-sided P value <0.05 was regarded as statistically significant. Missing categories were not included in these tests.

The primary endpoint was breast cancer as underlying cause of death. In addition to this, death from other cancers, death from other causes, and all causes were included in the main analysis. The distribution of the above mortality-related factors was examined in different groups defined by vital status and cause of death. These distributions were tested using the χ^2 test as described earlier for smoking.

Each woman was followed from baseline until the end of follow-up, 31 December 2010, or until she died. Mean follow-up was 24.1 years (s.d. 5.3) and total follow-up included 52 579 person-years. A Cox's proportional hazards analysis was used to estimate hazard ratios (HRs) with a confidence interval (CI) of 95% in relation to T_3 levels. T_3 levels were introduced as a continuous variable in the main analyses. T_3 was not normally distributed ($P<0.001$ using a one sample Kolmogorov-Smirnov test), but to give estimates more readily interpretable, the original T_3 values were used to obtain HRs. However, T_3 values were also transformed using the natural logarithm in order to confirm whether the associations were statistically significant or not. Analyses were adjusted first for age at baseline and in a final model for all potential confounders. The limited number of breast cancer deaths did not allow inclusion of all covariates in the same model, but in relation to this endpoint, age and one additional factor at a time were included in the final model. In this way, a maximum of three variables were included in each model. In tables, only the model with the largest change from the crude HR for T_3 was reported. The primary endpoint, breast cancer as cause of death, was also

analyzed with T₃ as a continuous variable stratified for menopausal status as we, in our previous study on T₃ levels and breast cancer incidence, found that the association was considerably stronger in postmenopausal women compared with premenopausal. The stratified analyses did only allow the inclusion of one additional covariate, and we considered age at baseline to be most important. The stratified analyses were further evaluated by including a term for interaction in the model between T₃ levels and menopausal status. A *P* value <0.05 was considered as a statistically significant interaction. Finally, breast cancer death was analyzed in relation to different T₃ quartiles where breast cancer-specific mortality was calculated per 10 000 person-years. Corresponding HRs were calculated as earlier.

It is possible that subclinical disease may affect T₃ levels, and in a sensitivity analysis, all analyses were repeated excluding all women who died before 2 years following baseline examination. SPSS version 18.0 (Lund, Sweden) was used for all analyses.

Results

Women in higher T₃ quartiles were relatively old ($\tau_b=0.29$; *P*<0.001), they had a lower educational level ($\tau_b=-0.10$; *P*<0.001), a lower alcohol

consumption ($\tau_b=-0.07$; *P*<0.001), and they were more often overweight than women in lower T₃ quartiles ($\tau_b=0.17$; *P*<0.001; Table 1). There was no statistically significant association between T₃ levels and smoking (overall *P*=0.82).

Women who died from cancers other than breast cancer, or from causes other than cancer, were considerably older at baseline compared with women alive at the end of follow-up (*P*<0.001; Table 2). Women who died from causes other than cancer during follow-up had a lower educational level (*P*=0.006), reported a lower alcohol consumption (*P*=0.03), and had a higher BMI (*P*<0.001) than women alive at the end of follow-up. Current smoking was more common among women who died from cancers other than breast cancer, and all causes other than cancer, compared with women alive at the end of follow-up (*P*<0.001).

In this study, we observed a positive association between T₃ levels and the risk of death from breast cancer (Table 3). The crude analysis did not reach statistical significance, but the risk increased following adjustment for age and other potential confounders. This association with mortality from breast cancer was only apparent among postmenopausal women compared with premenopausal. However, the terms for interaction between T₃ levels and menopausal status did not reach statistical significance. All statistically significant results in the continuous analyses were

Table 1 Distribution of potential determinants for mortality according to serum T₃ level. Column percent *P* values are given in italics.

Factor	T ₃ quartile (T ₃ range (mIU/l))					Kendall's τ -b coefficient (τ_b ; <i>P</i> values)
	1 (<i>n</i> =494 (<1.50))	2 (<i>n</i> =704 (1.60–1.80))	3 (<i>n</i> =456 (1.90–2.00))	4 (<i>n</i> =531 (2.10–4.30))	All (<i>n</i> =2185 (0.60–4.30))	
Age						
<50 years	62.1	46.6	26.1	21.5	39.7	0.29
>50 years	37.9	53.4	73.9	78.5	60.3	(<0.001)
Education						
Missing	4.5	4.1	4.2	3.2	4.0	–
<12 years	53.0	53.6	62.5	64.2	57.9	–0.10
12 years	20.9	27.4	22.1	21.8	23.5	(<0.001)
>12 years	21.7	14.9	11.2	10.7	14.5	
Smoking						
Missing	–	–	0.4	0.9	0.3	–
Never	43.5	47.7	47.6	47.1	46.6	(0.82) ^a
Current	35.8	33.2	34.0	33.1	34.0	
Ex	20.6	19.0	18.0	18.8	19.1	
<i>P</i> value ^b	Ref.	1.08	1.14	1.32	–	
Alcohol consumption						
Missing	–	0.1	0.4	1.5	0.5	–
Nothing	14.2	14.1	13.2	19.0	15.1	–0.07
Less than every week	55.3	60.7	62.5	60.1	59.7	(<0.001)
Every week	30.6	25.1	23.9	19.4	24.7	
BMI (kg/m ²)						
<20	14.8	10.1	7.9	7.5	10.1	0.17
≥20–<25	62.3	56.1	53.9	46.5	54.7	(<0.001)
≥25–<30	17.0	26.1	27.9	30.5	25.5	
≥30	5.9	7.7	10.3	15.4	9.7	

^aOverall *P* value from the χ^2 test. Not including missing values.

^bPairwise χ^2 tests, with corrected *P* values (multiplied with 3). Not including missing values.

Table 2 Distribution of potential determinants for mortality according to vital status. Column percent *P* values are given in italics.

Factor	Alive (<i>n</i> =1714)	Dead from breast cancer (<i>n</i> =26)	Dead from other cancers (<i>n</i> =182)	Dead from other causes (<i>n</i> =263)	Dead from all causes (<i>n</i> =471)	χ^2 , <i>P</i> value ^a
Age						
<50 years	44.1	65.4	24.2	19.4	23.8	<i><0.001</i>
>50 years	55.9	34.6	75.8	80.6	76.2	
<i>P</i> value ^b	Ref.	<i>0.09</i>	<i><0.001</i>	<i><0.001</i>	–	
Education						
Missing	2.8	0.0	8.2	9.1	8.3	–
<12 years	56.4	69.2	63.2	62.7	63.3	<i>0.003</i>
12 years	24.6	19.2	19.8	19.4	19.5	
>12 years	16.2	11.5	8.8	8.7	8.9	
<i>P</i> value ^b	Ref.	<i>1.53</i>	<i>0.39</i>	<i>0.006</i>	–	
Smoking						
Missing	0.4	0.0	0.5	–	0.2	–
Never	49.5	46.2	35.7	35.4	36.1	<i><0.001</i>
Current	30.2	23.1	47.8	50.2	47.8	
Ex	20.0	30.8	15.9	14.4	15.9	
<i>P</i> value ^b	Ref.	<i>1.14</i>	<i><0.001</i>	<i><0.001</i>	–	
Alcohol consumption						
Missing	0.6	0.0	0.5	–	0.2	–
Nothing	14.2	26.9	12.6	21.3	18.3	<i>0.04</i>
Less than every week	59.9	50.0	63.2	57.0	59.0	
Every week	25.3	23.1	23.6	21.7	22.5	
<i>P</i> value ^b	Ref.	<i>0.57</i>	<i>2.01</i>	<i>0.03</i>	–	
BMI (kg/m ²)						
<20	9.9	7.7	9.3	11.8	10.6	<i>0.004</i>
≥20–<25	56.8	50.0	50.5	44.5	47.1	
≥25–<30	24.6	34.6	29.1	27.8	28.7	
≥30	8.6	7.7	11.0	16.0	13.6	
<i>P</i> value ^b	Ref.	<i>2.13</i>	<i>0.93</i>	<i><0.001</i>	–	

^aOverall *P* value from the χ^2 test tested for alive/dead from breast cancer/dead from other cancers/dead from other causes. Not including missing values.

^bPairwise χ^2 tests, with corrected *P* values (multiplied with 3). Not including missing values.

confirmed using the logarithmic T_3 value (data not shown). In the quartile analysis, the risk of breast cancer death was higher in the fourth T_3 quartile compared with the first quartile (Table 4). The limited number of events did not allow a quartile analysis stratified for menopausal status.

The risk of deaths from cancers other than breast cancer, causes other than breast cancer, and all causes were positively associated with T_3 levels in the unadjusted analyses (Table 3). However, following adjustment for age, and subsequently for all potential confounders, these estimates were close to unity. When

Table 3 Mortality in relation to serum T_3 levels. The model with the largest influence on the HR, compared with the crude model, included alcohol consumption in addition to age at baseline; HR and corresponding *P* values presented in table. All these multivariate models showed statistically significant HRs for T_3 .

Cause of death	Subjects in analysis (<i>n</i>)	Dead (<i>n</i>)	HR (95% CI), crude T_3	<i>P</i> value, T_3	HR (95% CI), age-adjusted T_3	<i>P</i> value, T_3	HR (95% CI), adjusted ^a T_3	<i>P</i> , value T_3
Breast cancer								
All	2185	26	2.22 (0.92–5.37)	<i>0.077</i>	2.80 (1.26–6.25)	<i>0.012</i>	2.82 ^b (1.25–6.37)	<i>0.01^b</i>
Premenopausal ^c	863	14	0.81 (0.17–3.76)	<i>0.784</i>	0.93 (0.20–4.37)	<i>0.930</i>	–	–
Postmenopausal ^c	1322	12	4.30 ^d (1.88–9.86)	<i>0.001</i>	3.73 ^e (1.69–8.22)	<i>0.001</i>	–	–
Other cancers	2185	182	1.45 (0.99–2.11)	<i>0.055</i>	1.09 (0.72–1.65)	<i>0.685</i>	0.98 (0.64–1.51)	<i>0.937</i>
Other causes	2185	445	1.60 (1.26–2.02)	<i><0.001</i>	1.17 (0.90–1.52)	<i>0.237</i>	1.07 (0.82–1.41)	<i>0.610</i>
All causes	2185	471	1.63 (1.30–2.05)	<i><0.001</i>	1.25 (0.97–1.60)	<i>0.087</i>	1.16 (0.89–1.50)	<i>0.280</i>

^aAdjusted for age at baseline, educational level, smoking status, alcohol consumption, and BMI (continuous).

^bAdjusted for age at baseline and one factor at a time out of educational level, smoking status, alcohol consumption, and BMI (continuous).

^cMenopausal status at baseline.

^dInteraction between T_3 and menopausal status: *P* value=0.07.

^eInteraction between T_3 and menopausal status: *P* value=0.12.

Table 4 Breast cancer-specific mortality in relation to serum T₃ levels. The model with the largest influence on the HR for the fourth quartile, compared with the crude model, included smoking status in addition to age at baseline; HR and corresponding *P* value presented in table. All these multivariate models showed statistically significant HRs for the fourth T₃ quartile, except for the model including age at baseline and BMI where this association was only borderline significant (*P*=0.05002).

T ₃ (quartile)	Subjects (<i>n</i>)	Dead from breast cancer (<i>n</i>)	Mortality/10 000 person-years	HR (95% CI), crude T ₃	HR (95% CI), age-adjusted T ₃	HR ^a (95% CI), adjusted T ₃
1	494	4	3.2	1.00	1.00	1.00
2	704	10	5.8	1.82 (0.57–5.81)	2.07 (0.65–6.63)	2.07 (0.65–6.61)
3	456	3	2.8	0.91 (0.20–4.05)	1.27 (0.28–5.77)	1.27 (0.28–5.76)
4	531	9	7.4	2.48 (0.76–8.09)	3.61 (1.08–12.1)	3.65 (1.09–12.2)
Total	2185	26	4.9	–	–	–
Overall <i>P</i> value	–	–	–	0.30	0.15	0.14

^aAdjusted for age at baseline and one factor at a time out of educational level, smoking status, alcohol consumption, and BMI (continuous).

women who died within 2 years following baseline were excluded from the analyses, all results were similar (data not shown).

Discussion

This is the first prospective study on T₃ levels in relation to breast cancer mortality. It shows that pre-diagnostic T₃ levels are positively associated with the risk of breast cancer-specific death and that this is not related to a general effect on cancer death or all-cause mortality.

It may be asked whether breast cancer cases in this cohort are representative of the whole breast cancer population. This cohort mainly comprised middle-aged women and 70% of the women invited to the health examination attended (9). As we have no information about exposure to the studied risk factors in women outside this cohort, absolute risks may not be applicable to all age groups or to the general population. However, as there was a wide distribution of T₃ levels, it was possible to make internal comparisons between subjects with relatively low and high values respectively. Hence, we consider that our estimates of relative risks were not considerably affected by selection bias.

Incomplete follow-up may affect the results. However, the Swedish Cause-of-Death Registry has been validated and found to have a completeness of about 97.3% in 2008 (11). Moreover, correctness of cause of death due to malignancies has been shown to be higher than 90% in the Swedish Cause-of-Death Registry (12).

Subjects with elevated T₃ levels may already be within the health care system, possibly because of related symptoms, and due to this, the diagnosis of breast cancer might be established earlier than for euthyroid subjects. If true, this would lead to early diagnosis and an expected decrease in breast cancer mortality in this group. However, this is not likely as the contrary was found in this study. Furthermore, general mammography screening was introduced in Sweden in 1991 and stands for the majority of detection of breast cancer cases (13). It is also unlikely that thyroid status does affect participation in mammography screening. It should

also be noted that most women with T₃ levels in the fourth quartile in this study still had levels within the normal range, and these women probably did not have any symptoms of thyroid disease. It is not likely that the results in this study were due to a detection bias.

The method of analysis for T₃ remained the same throughout the study period and all analyses were performed using a standardized collection of blood samples. T₃ levels were analyzed following blood collection in 1983, 1984 and between 1990 and 1992. There are no recorded values for the coefficient of variance (CV) from the laboratory covering this period. However, reported within-laboratory CV at the time for T₃ were in the order of 9–11% according to a large European analysis including 150 laboratories (14). Following this, we consider that T₃ levels had a good reliability and that misclassification was probably low.

It is also important to consider true variation in T₃ values as there is a well-known circadian and seasonal variation (15). Tracking of individuals, that is ranking of individuals over time, is, however, quite stable (16), and a true variation over time would most likely have led to an undifferential misclassification of T₃ and, hence, attenuated risks.

The current study is the largest prospective study to date on thyroid hormone levels and breast cancer mortality, but the number of deaths due to breast cancer was still very limited. CIs were wide and the statistical power was relatively low. This led to an imprecision in the estimates related to T₃ and breast cancer mortality. This was specifically apparent in the quartile analysis where CI was very wide, and the overall *P* value did not reach statistical significance. Moreover, statistical power was an even more serious problem in analyses stratified for menopausal status, and these results, although statistically significant, should be regarded with caution.

An additional problem related to the limited number of breast cancer deaths was that not all confounders could be included at the same time in the final model for this endpoint. However, the models including age at baseline and one additional factor yielded statistically significant positive associations between T₃ levels and

breast cancer death; this indicates that these factors did not seriously confound the observed association.

Concerning death from cancers other than breast cancer, death from causes other than breast cancer, and all-cause mortality, there were a substantially larger number of events, and we consider that the lack of any strong associations was not merely the result of poor statistical power, i.e. a type II error.

In order to simplify the interpretation of HR obtained in the continuous analysis, we used original values even if they were not normally distributed. However, all statistically significant results in the continuous analyses were confirmed using the logarithmic T_3 value. This is also what would be expected given the high correlation between raw and log-transformed T_3 values.

The potential association between thyroid hormones and outcome following breast cancer has been discussed for more than a century. Several early studies used thyroid hormones/extracts as breast cancer treatment, but the effect was not apparent (2). We have found that no studies were published during the last 50 years on this topic. Goldman *et al.* (8), the only study on thyroid conditions and breast cancer mortality, found no excess risk of breast cancer death in women with thyroid disorders. Smyth *et al.* (17) followed 195 breast cancer patients and they found that positive TPO-Ab status was associated with a favorable survival, i.e. a lower risk of recurrent disease and death. Fiore *et al.* (6) examined 47 patients, among whom 16 died, and also found that positive thyroid antibody status (TPO-Ab and/or Tg-Ab) was associated with a low mortality, i.e. a good survival. These findings on recurrence-free survival and overall survival in relation to TPO-Ab status were not confirmed by Jiskra *et al.* (7), including 84 patients where 11 died. Fiore *et al.* (6) and Jiskra *et al.* (7) also investigated T_4 levels and TSH in relation to overall survival, but they found no clear associations. A problem in the interpretation of the above studies is that thyroid hormones, TSH and TPO-Ab, may indeed be affected by prevalent breast cancer, stress, or treatment. Generally, previous studies have been hampered by a low number of cases and short follow-up, and we have found no study on pre-diagnostic thyroid function and survival following breast cancer. Concerning mortality, no study has investigated thyroid function or T_3 levels in relation to breast cancer-specific mortality in a 'breast cancer healthy' population.

All-cause mortality was associated with relatively high T_3 levels in the crude analysis, but adjusted for age and other potential confounders, all estimates were close to unity. There are several recent meta-analyses and reviews on the potential association between thyroid conditions and all-cause mortality. Overt hyperthyroidism was associated with a slightly increased risk of all-cause mortality (RR=1.21:1.05–1.38) in a meta-analysis by Brandt *et al.* (18), including more than 30 000 patients. All the included studies were adjusted for age, but none for education, BMI, or alcohol

consumption, and only some for smoking. Considering subclinical conditions, subclinical hyperthyroidism was positively associated with all-cause mortality in a meta-analysis of seven cohort studies (HR = 1.41:1.12–1.79) using a general population as reference (19). Interestingly, another meta-analysis including ten prospective studies found no statistically significant association between subclinical hyperthyroidism and all-cause mortality (20). This study excluded subjects with goiter, and even in the highest quartile, most subjects were within the reference limits for T_3 . All in all, this makes it difficult to compare our results to studies based on overt thyroid conditions. Some of the previous studies also included patients treated with T_4 ; that is, these studies may reflect an effect caused by exposure to exogenous hormones.

The biological mechanism explaining the association of T_3 levels and breast cancer-specific mortality is not clear. However, the presence of thyroid hormone receptors in human breast and breast cancer cell lines has been established (21, 22, 23, 24), and the proliferative effect of T_3 has been confirmed by various experimental studies on breast cancer. Our findings are in line with these data (25, 26, 27, 28).

It has been shown that T_3 binds and stimulates the estrogen receptor, acting in synergy with estrogen on breast cancer cell lines, potentiating the estrogenic effect, and enhancing cell proliferation (29). The role of estrogen in carcinogenesis of the breast is well known and the possibility that this effect may be even stronger in conjunction with relatively high levels of T_3 could in part explain the results in this study.

The positive association between T_3 and breast cancer was specifically strong in postmenopausal women. Therefore, an imbalance between estrogen and T_3 with an increased T_3 /estradiol ratio may be more important than a pure synergistic effect between these two hormones for the risk of developing breast cancer. It has been suggested that this imbalance might enhance breast cancer development (25). This theory is in accordance with our findings that T_3 levels in postmenopausal women are positively associated with breast cancer mortality. An important issue for future studies will be to evaluate the widespread, long-term use of T_4 treatment in TSH-suppressive doses for benign thyroid disease (30, 31), and the management of women with subclinical hyperthyroidism (32, 33, 34). Such studies will contribute with important evidence whether or not to treat mild and/or subclinical thyroid disorders.

Conclusions

In conclusion, the present prospective cohort study, the first of its kind on prospectively measured T_3 levels, indicates that T_3 levels are positively associated with breast cancer-specific mortality and that this is not related to a general effect on all-cause mortality.

Declaration of interest

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

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