Thyroid-Stimulating Hormone, Thyroglobulin, and Thyroid Hormones and Risk of Differentiated Thyroid Carcinoma: The EPIC Study


Background

Increased levels of thyroglobulin (Tg) and thyroid-stimulating hormone (TSH) are associated with differentiated thyroid carcinoma (TC) risk, but strong epidemiological evidence is lacking.

Methods

Three hundred fifty-seven incident TC case patients (n = 300 women and 57 men; mean age at blood collection = 51.5 years) were identified in the EPIC cohort study and matched with 2 (women) or 3 (men) control subjects using incidence density sampling. Matching included study center, sex, age, date, time, and fasting status at blood collection. Levels of total and free (f) thyroxine (T4) and triiodo-thyronine (T3), TSH, Tg, and anti-Tg antibodies (TgAb) were measured by commercially available immunoassays. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using conditional logistic regression. All statistical tests were two-sided.

Results

TC risk was positively associated with Tg (OR for the highest vs lowest quartile = 9.15; 95% CI = 5.28 to 15.90; P < .001) and negatively associated with TSH level (OR = 0.56; 95% CI = 0.38 to 0.81; P = .001). Odds ratios were not modified by adjustment for weight and height and were consistent across sexes, age groups, and countries. The association with Tg was stronger in follicular than papillary TC. The odds ratio for TgAb-positivity was 1.50 (95% CI = 1.05 to 2.15; P = .03). Among case patients, TSH level was stable over time, whereas Tg level was higher in proximity to TC diagnosis. Areas under the receiver operating characteristic curve were 57% and 74% for TSH and Tg level, respectively.

Conclusions

High Tg levels precede by up to 8 years the detection of TC, pointing to a long sojourn time of the disease. Low TSH levels may predispose to TC onset. Neither marker has sufficient accuracy to be a screening test.


Thyroid cancer incidence has been increasing over the last two or three decades in high-resource countries (1,2) in which the disease is currently the second most frequent cancer, after breast cancer, in women younger than 45 years (3). In high-resource countries, papillary and follicular carcinomas, known collectively as differentiated thyroid carcinoma (TC), account for approximately 75% and 13% of thyroid cancer, respectively (1,2). The only well-established risk factors for TC are exposure to ionizing radiation, especially during childhood (4), and history of goiter and thyroid adenoma (5,6). Associations with hypo- or hyperthyroidism and thyrotoxicosis are weaker and less consistent (5,6). Moderate positive associations between TC risk and weight and height have also been reported (7,8).

The thyroid gland mainly consists of follicular cells surrounding a lumen, which contains thyroglobulin (Tg), a receptor protein for iodine. The synthesis of thyroid hormones (ie, thyroxine [T4] and triiodo-thyronine [T3]) depends on the availability of adequate quantities of iodine and Tg (9). Thyroid function is regulated by thyroid-stimulating hormone (TSH), which is secreted by the anterior pituitary gland.

In this article, we took advantage of the European Prospective Investigation into Cancer and Nutrition cohort (EPIC) to assess the association between TC risk and prediagnostic levels of TSH, Tg, and thyroid hormones in a 10-fold larger number of case patients than in the only previous prospective study on the topic (10).
Methods

Study Population, Blood Sample Collection, and Follow-Up

The EPIC cohort consists of approximately 370,000 women and 150,000 men aged 35 to 69 years when recruited between 1992 and 1998 in 23 centers in 10 European countries (Denmark; France; Germany; Greece; Italy; Norway; Spain; Sweden; the Netherlands; and the United Kingdom) (11,12). Extensive standardized questionnaires were collected on habitual diet and lifestyle variables (12).

Blood samples (30 mL) were aliquoted into 0.5-mL straws of serum, plasma, red blood cells, anduffy coat. In France, Germany, Greece, Italy, Norway, Spain, the Netherlands, and the United Kingdom, half of the samples for each participant were stored locally and half were stored at the International Agency for Research on Cancer (IARC), Lyon, France, in liquid nitrogen containers (−196°C) (11,12). In Denmark and Sweden, samples were stored in liquid nitrogen vapors (−150°C) and in −80°C freezers, respectively.

In most EPIC centers, incident cases of cancer are identified through record linkage with regional cancer registries. In France, Germany, and Greece, follow-up for cancer incidence is based on a combination of methods, including medical records and active follow-up. Capture dates for this study were defined as the latest date of complete follow-up for both cancer incidence and vital status (i.e., between December 31, 2007, and December 31, 2009 in most centers and December 2006 in France).

Nested Case–Control Design

Case patients were defined as participants who developed TC after enrollment in the EPIC study and before the end of the follow-up. Participants were excluded if they reported a history of cancer other than nonmelanoma skin cancer. Thyroid cancer case patients with rare histological types (28 medullary, 6 anaplastic, and 3 other morphologies, and 1 lymphoma) were not included. A blood sample was not available for one man and 208 women with TC, of whom 78% were from the women-only cohort from France, in which blood collection started later. In total, 357 TC case patients were included (262 papillary, 58 follicular, and 37 not otherwise specified TC, which are likely to also be papillary TC). Tumor stage, node, and metastasis (TNM) stage was known for 52% of female and 49% of male case patients.

For each TC case patient, two control subjects for women, and three control subjects for men were randomly chosen among cancer-free cohort participants by incidence density sampling. Matching criteria were study center, sex, age (±1 year), date (±3 months), time (±1 hour), fasting status (≤3 hours; 3–6 hours; >6 hours) at blood collection, and duration of follow-up. Menopausal status (pre-, post-, perimenopausal, and unknown menopausal status) (13); female hormone use at blood donation; and, if premenopausal, phase of the menstrual cycle were additional matching variables in women. Phases of the menstrual cycle were classified as follicular, periovulatory, or luteal in the same way as previously described (14).

All EPIC participants gave their written informed consent for the use of their blood samples for research. This study on TC was further approved by the ethics committees of IARC and all participating centers.

Laboratory Assays

Sera were used for laboratory assays except in Norway (citrated plasma) and Umeå, Sweden (ethylenediaminetetraacetic acid or edetic acid plasma). Total and free (T) T3 and T4 were measured by direct radioimmunoassay; TSH was measured by direct immunoradiometric assays (Beckmann Coulter, Marseille, France); and Tg and anti-Tg antibodies (TgAb) were measured by immunoradiometric assays from DiaSorin (Saluggia, Italy).

All assays were performed at the IARC without knowing case/control status. TSH, FT3 and FT4, and total T3 and T4 were measured on never-thawed samples, whereas Tg and TgAb were measured on samples that had been thawed and frozen once. Samples belonging to matched case–control sets were always tested in the same batch. Based on results obtained for quality-control samples, intra-batch coefficients of variation ranged between 2.2% (Tg) and 6.5% (T3). Among control subjects, the 5th to 95th percentile range of each assay was consistent with the reference range provided by the manufacturer for euthyroid individuals not receiving thyroid medications. Sixty-two TC case patients and 92 control subjects were TgAb positive (TgAb level > 100 IU/mL) and were excluded from Tg analyses because the presence of TgAb interferes with Tg determination in immunoradiometric assays. Sensitivity analyses in which the TgAb cutpoint was set between 80 and 120 IU/mL yielded similar findings, as did the inclusion of TgAb-positive individuals (data not shown).

Statistical Analyses

Quartile categories were based on the distribution of the level of TSH, Tg, and thyroid hormones among control subjects in women and men separately.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed using conditional logistic regression to take into account the matching design (PHREG procedure of the SAS software package, version 9, SAS, Cary, NC). Odds ratios were conditioned on matching variables and further adjusted for weight and height (as continuous variables). Odds ratios are shown for the two sexes combined because, despite slight differences in thyroid hormone levels, correlation coefficients and odds ratios were very similar in women and men. Tests for a trend in odds ratio by quartile categories of hormone level were computed by assigning the same batch. Based on results obtained for quality-control samples, intra-batch coefficients of variation ranged between 2.2% (Tg) and 6.5% (T3). Among control subjects, the 5th to 95th percentile range of each assay was consistent with the reference range provided by the manufacturer for euthyroid individuals not receiving thyroid medications. Sixty-two TC case patients and 92 control subjects were TgAb positive (TgAb level > 100 IU/mL) and were excluded from Tg analyses because the presence of TgAb interferes with Tg determination in immunoradiometric assays. Sensitivity analyses in which the TgAb cutpoint was set between 80 and 120 IU/mL yielded similar findings, as did the inclusion of TgAb-positive individuals (data not shown).

For TSH and Tg, heterogeneity of TC risk by selected cofactors was investigated using a forest plot. Odds ratios in the forest plot were derived from a trend model using quartile scores of TSH and Tg as continuous variables. P values for heterogeneity were derived by testing an interaction term between the quartile score and the cofactor. If the cofactor was ordinal (e.g., age) then the interaction was a test of trend in the odds ratio, whereas for nonordered cofactors (e.g., country) it was a test for differences.

The dose–response relationship between TC and TSH or Tg was further investigated using the log-transformed hormone measurements instead of the quartiles. A natural cubic model was fit, and the likelihood ratio test was used to test the fit of the model to the data. The likelihood ratio test was used to test for trends in the odds ratio by quartile categories of hormone level.
spline was fitted in the conditional logistic regression model
using knots at the 20, 40, 60, and 80 percentiles of the distribu-
tion in control subjects (men and women combined), with
boundary knots at the 5 and 95 percentiles (15). Estimates for
TSH were based on a joint spline model for TSH and Tg, with
adjustment for anti-TgAb positivity. Estimates for Tg were
based on a joint spline model for Tg and TSH, restricted to
participants who were anti-TgAb negative. For both TSH and
Tg, the reference level for a relative risk of 1 was taken to be
the median hormone level in control subjects. All statistical
tests were two-sided.

Receiver operating characteristic (ROC) curves (16) showing
sensitivity as a function of specificity were calculated for TSH and
Tg levels to evaluate the potential accuracy of the two markers
as screening tests for TC. These ROC curves were adjusted for
matching by center, sex, and age (in 5-year groups) (17). The ability
of TSH and Tg to discriminate between individuals who devel-
oped TC or not is summarized by the area under the curve (AUC),
with an AUC of 100% being the best possible test and an AUC of
50% corresponding to a random test with no discriminatory power.
Confidence intervals for the AUC were calculated by drawing 2000
bootstrap samples.

Table 1. Comparison of case patients with differentiated thyroid carcinoma and their matched control subjects by selected characteristics separately in women and men

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at blood collection, y†</td>
<td>51.4 (38.0–64.5)</td>
<td>51.4 (37.7–64.9)</td>
<td>Matched</td>
</tr>
<tr>
<td>Age at diagnosis, y†</td>
<td>57.8 (44.3–70.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Years between blood collection and diagnosis†</td>
<td>6.4 (1.5–12.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Height, cm†</td>
<td>161.5 (150.2–171.5)</td>
<td>160.3 (149.9–171.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Weight, kg†</td>
<td>67.8 (52.5–89.3)</td>
<td>65.7 (50.7–88.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Waist-to-hip ratio†</td>
<td>0.80 (0.71–0.92)</td>
<td>0.79 (0.70–0.91)</td>
<td>.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²†</td>
<td>26.0 (20.2–33.8)</td>
<td>25.6 (19.8–34.2)</td>
<td>.23</td>
</tr>
<tr>
<td>Smoking status, %‡</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>56.6</td>
<td>60.8</td>
<td>.39</td>
</tr>
<tr>
<td>Former smoker</td>
<td>22.5</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.9</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>Education level, %‡</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>None or primary</td>
<td>41.8</td>
<td>40.4</td>
<td>.76</td>
</tr>
<tr>
<td>Secondary or more</td>
<td>58.2</td>
<td>59.6</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Prediagnostic levels of thyroid-stimulating hormone, thyroglobulin, and thyroid hormones in case patients with differentiated thyroid carcinoma and their matched control subjects, separately in women and men*

<table>
<thead>
<tr>
<th>Levels</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH, mIU/L</td>
<td>299</td>
<td>299</td>
<td>300</td>
</tr>
<tr>
<td>Tg, ng/mL†</td>
<td>241</td>
<td>241</td>
<td>259</td>
</tr>
<tr>
<td>fT3, pmol/L</td>
<td>294</td>
<td>294</td>
<td>294</td>
</tr>
<tr>
<td>T3, nmol/L</td>
<td>296</td>
<td>296</td>
<td>296</td>
</tr>
<tr>
<td>T4, nmol/L</td>
<td>291</td>
<td>291</td>
<td>291</td>
</tr>
</tbody>
</table>

* Paired t tests between case patient vs average of values in two (women) or three (men) matched control subjects. For categorical variables, the statistical significance of case/control differences was tested using paired χ² test. All statistical tests were two-sided.
† Mean (5th–95th) percentiles.
‡ Percentages excluding participants with missing variables.

fT3 = free triiodo-thyronine; fT4 = free thyroxine; T3 = triiodo-thyronine; T4 = thyroxine; Tg = thyroglobulin; TSH = thyroid-stimulating hormone.
† Wilcoxon signed rank sum test; all statistical tests were two-sided.
‡ Thyroglobulin antibody–positive individuals were excluded.
Results

Table 1 shows a comparison of TC case patients and their matched control subjects by selected characteristics, separately for women and men. Mean age at blood collection (mean = 51.5 years) and at TC diagnosis (mean = 58 years) and number of years between blood collection and TC diagnosis (mean = 6.4 years) were similar in women and men. In women, TC cases were taller (P = .002), were heavier (P = .001), and had a larger waist-to-hip ratio (P = .03) than their matched controls.

Median prediagnostic levels and other quantiles of the distribution of TSH, Tg, and thyroid hormones by case/control status and sex are shown in Table 2. In both men and women, TSH levels were lower (P = .01 for men and P = .05 for women) and Tg levels were higher (P < .001 for both sexes) in TC cases than in their matched controls. In women, median fT3 levels were similar in case patients and control subjects, but the lower tail of the distribution was longer in control subjects than case patients, leading to a statistically significant difference (P = .04). No statistically significant differences were observed for fT3 in men and for T3, fT4, and T4 in either sex.

Spearman's correlation coefficients between the levels of TSH, Tg, and thyroid hormones in women and men combined were computed (data not shown). The strongest positive correlations were found between fT3 and fT4; fT3 and T3; fT4 and T4; and T3 and T4. TSH levels were negatively correlated with those of fT4 and T4 (Spearman’s r = −0.22 and −0.16, respectively), whereas Tg levels were not correlated with those of either thyroid hormones or TSH.

TC risk was negatively associated with TSH level (OR for the highest vs lowest quartile = 0.56; 95% CI = 0.38 to 0.81; P = .001) but positively and strongly associated with Tg level (OR = 9.15; 95% CI = 5.28 to 15.90; P < .001) (Table 3). TC risk was also higher in the second and fourth quartile groups compared to the lowest quartile group, but there was no statistically significant linear trend (P_{trend} = .10). TgAb-positive individuals had an odds ratio of 1.50 (95% CI = 1.05 to 2.15; P = .03). T3, fT4, and T4 were not related to TC risk. Adjustment for weight and height did not modify any of the odds ratios in Table 3.

Table 3. Odds ratios, adjusted or not for weight and height, for differentiated thyroid carcinoma and corresponding 95% confidence interval by quartile of thyroid-stimulating hormone, thyroglobulin, thyroid hormones, and presence of antithyroglobulin antibodies in men and women combined*

<table>
<thead>
<tr>
<th>Estimates</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4 (highest)</th>
<th>P (_trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>119/191</td>
<td>95/190</td>
<td>69/191</td>
<td>73/190</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>0.77 (0.55 to 1.08)</td>
<td>0.54 (0.38 to 0.79)</td>
<td>0.56 (0.38 to 0.81)</td>
<td>.001</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>0.79 (0.56 to 1.11)</td>
<td>0.54 (0.37 to 0.78)</td>
<td>0.55 (0.37 to 0.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Tg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls§</td>
<td>22/140</td>
<td>31/140</td>
<td>42/140</td>
<td>196/139</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>1.46 (0.78 to 2.74)</td>
<td>2.14 (1.18 to 3.89)</td>
<td>9.15 (5.28 to 15.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>1.46 (0.77 to 2.74)</td>
<td>2.17 (1.19 to 3.96)</td>
<td>8.79 (5.04 to 15.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>fT3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>68/190</td>
<td>105/189</td>
<td>84/189</td>
<td>96/189</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>1.68 (1.13 to 2.50)</td>
<td>1.39 (0.91 to 2.13)</td>
<td>1.69 (1.06 to 2.69)</td>
<td>.10</td>
</tr>
<tr>
<td>OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>1.64 (1.10 to 2.45)</td>
<td>1.32 (0.86 to 2.03)</td>
<td>1.65 (1.03 to 2.63)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>81/185</td>
<td>90/185</td>
<td>80/185</td>
<td>99/184</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>1.11 (0.77 to 1.60)</td>
<td>1.02 (0.68 to 1.52)</td>
<td>1.29 (0.87 to 1.92)</td>
<td>.27</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>1.12 (0.77 to 1.62)</td>
<td>1.00 (0.67 to 1.50)</td>
<td>1.22 (0.92 to 1.63)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>fT4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>98/189</td>
<td>81/188</td>
<td>89/189</td>
<td>84/188</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>0.82 (0.57 to 1.28)</td>
<td>0.89 (0.62 to 1.28)</td>
<td>0.86 (0.58 to 1.28)</td>
<td>.55</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>0.83 (0.58 to 1.20)</td>
<td>0.91 (0.63 to 1.32)</td>
<td>0.87 (0.59 to 1.30)</td>
<td>.62</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>94/182</td>
<td>65/181</td>
<td>107/182</td>
<td>80/181</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>0.70 (0.48 to 1.02)</td>
<td>1.17 (0.82 to 1.67)</td>
<td>0.86 (0.58 to 1.29)</td>
<td>.94</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>0.71 (0.48 to 1.04)</td>
<td>1.18 (0.82 to 1.68)</td>
<td>0.89 (0.59 to 1.33)</td>
<td>.84</td>
</tr>
<tr>
<td>**TgAb</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>292/666</td>
<td>62/92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)†</td>
<td>1.00 (referent)</td>
<td>1.50 (1.05 to 2.15)</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>ADJ OR (95% CI)‡</td>
<td>1.00 (referent)</td>
<td>1.51 (1.05 to 2.18)</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
</tbody>
</table>

* ADJ = adjusted; fT3 = free triiodo-thyronine; fT4 = free thyroxine; OR = odds ratios; Q = quartile; T4 = thyroxine; T3 = triiodo-thyronine; Tg = thyroglobulin; TSH = thyroid-stimulating hormone.
† From conditional logistic regression analyses, conditioned on EPIC recruitment center; sex; age at blood donation; date and time of the day at blood donation; fasting status; and, among women menopausal status, sex hormone use, and phase of menstrual cycle among premenopausal women. All statistical tests were two-sided.
‡ Further adjusted for height and weight.
§ Thyroglobulin antibody–positive individuals were excluded.
|| Binary variable (positive = thyroglobulin antibody ≥ 100 IU/mL).
Mutual adjustment of TSH, Tg, and TgAb did not substantially change the odds ratios, and no statistically significant interaction was found between TSH and Tg ($P = .51$) or between TSH and TgAb ($P = .84$) (data not shown). Continuous analyses of the relationship between thyroid cancer and TSH or Tg based on spline models (data not shown) confirmed the presence of an approximately linear dose–response curve as shown in quartile-based analyses.

No statistically significant heterogeneities in the association between TSH and Tg levels and TC risk were observed by sex, age at blood donation, country, education level, smoking, or TNM stage (Figure 1). The odds ratio for TSH did not vary by BMI.

![Figure 1](https://academic.oup.com/jnci/article-abstract/106/6/dju097/2606870)

**Figure 1.** Odds ratios (ORs) of differentiated thyroid carcinoma for an increase of 1 quartile of thyroid-stimulating hormone (TSH) and thyroglobulin (Tg), stratified by selected variables. BMI = body mass index; CI = confidence interval; TNM = tumor, node, metastasis staging system. $P$ indicates $P$ value for difference between strata; $P^*$ indicates $P$ value for trend by strata. All statistical tests were two-sided.
\(P = .58\), whereas the odds ratio for Tg was higher \((P = .05)\) among individuals with lower BMI (BMI <26 kg/m\(^2\): OR = 2.70, 95% CI = 2.11 to 3.45; BMI ≥26 kg/m\(^2\): OR = 1.93, 95% CI = 1.53 to 2.43). The positive association with Tg was stronger \((P = 0.03)\) for follicular TC (OR = 4.45; 95% CI = 2.31 to 8.56) than for papillary TC (OR = 2.10; 95% CI = 1.74 to 2.54). The odds ratio for TSH did not vary over time between blood collection and TC diagnosis. The odds ratio for Tg was highest less than 4 years before TC diagnosis, but there was no statistically significant trend with time \((P_{\text{trend}} = .12)\). (Figure 1).

Figure 2 shows that, among case patients, TSH levels were stable over the years before TC diagnosis \((P_{\text{trend}} = .57)\), whereas Tg levels were highest in case patients for whom blood had been collected in proximity to TC diagnosis \((P_{\text{trend}} = .002)\). Adjustment for age did not alter these findings.

Figure 3 shows the ability of TSH and Tg levels to distinguish individuals who developed TC or not. Areas under the curve were 57\% (95% CI = 51\% to 59\%) and 74\% (95% CI = 70\% to 77\%) for TSH and Tg, respectively. The sensitivity of Tg is, however, only 43\% (95% CI = 39\% to 50\%) if a specificity of 90\% is required. If sensitivity has to reach 80\%, the specificity of Tg test would drop to 42\% (95% CI = 34\% to 55\%).

Discussion

Our study showed a strong positive association between TC risk and prediagnostic blood levels of Tg. Individuals in the highest Tg quartile had a ninefold higher risk compared with those in the lowest quartile. TSH level was negatively associated with TC risk. The level of T3 and T4 and the corresponding free fractions were not associated with TC risk. Although a slightly lower risk was seen in individuals in the lowest fT3 quartile, there was no statistically significant trend \((P = .13)\).

Our findings on Tg confirm, on a much larger scale, those from the Janus Serum Bank, Norway \((10)\), which included 43 TC cases (36 papillary, 4 follicular, and 3 anaplastic). In our study, there was a statistically significant difference in Tg level between case patients and control subjects up to 8 years before TC diagnosis. However, the highest levels of Tg in TC case patients were observed in proximity to TC diagnosis. There was no statistically significant variation in the positive association with Tg level by sex, age, education, smoking, or TNM stage. No heterogeneity was found across EPIC countries either, despite large variations in TC incidence rates. The association with Tg level was, however, stronger in individuals who were not overweight and for follicular vs papillary TC.

The causes of elevated Tg levels in the preclinical phase of TC are unclear. Tg is the matrix protein for the synthesis of T3 and
T4 and one of the main antigens in autoimmune thyroid disease (18). The prolonged elevation of Tg level in TC case patients suggests enhanced secretion or leakage of Tg from a slowly growing thyroid tumor. High-resolution ultrasound can detect thyroid nodules in 19% to 67% of randomly selected individuals, with higher frequency in women and the elderly (19). In an autopsy study from Finland, 36 of 101 thyroids in children and adults younger than 40 years harbored one or more foci of papillary carcinoma (20).

The frequency of detection of TgAb in our study (17.5% of case patients and 12.1% of control subjects) is consistent with previous studies on TC patients (21) and a population-based survey in the United States (22), respectively. A number of clinic-based studies showed high TgAb levels in patients with Hashimoto's thyroiditis or TC (23).

The negative association of TSH level with TC risk in our study was consistently found in both categorical analyses and continuous analyses based on a spline-model that could confirm a lack of U-shaped dose–response. The negative association was not modified by adjustment for weight, height, Tg levels, and positivity for TgAb. Contrary to Tg findings, TSH levels in TC case patients did not increase with the proximity to TC diagnosis. High TSH levels also appeared to predispose to TC onset consistently in different strata of individuals' and TCs characteristics and in different EPIC countries.

TSH is the major growth factor for thyroid follicular cells, and TSH suppression is a mainstay of clinical TC management (24). A meta-analysis (24) showed that higher TSH level was associated with increased TC risk, but all 22 eligible studies were cross-sectional studies, and the control group always consisted of patients with thyroid nodules or patients undergoing surgical treatment for a suspicion of TC. Some nodules can produce high levels of thyroid hormone and, hence, induce low TSH levels. No association between TC risk and TSH levels was found in the small population-based cohort study from Norway (10). Our study is, therefore, the first to evaluate on a large scale whether TSH level affects TC risk in a healthy population.

A negative association between TSH level and TC risk is indirectly supported by recent studies of genetic predisposition. Genome-wide association studies of TC have found two common variants located on 9q22.23 and 14q13.3 that have also been shown to be associated with low TSH levels. A further three variants associated with TC risk on 2q35, 8p12 and 14q13.3 have been found by first conducting a genome-wide association study of low TSH and then confirming an association with cancer in case–control studies of TC (25). Gudmundsson et al. (25) suggested that low TSH levels could lead to less differentiation of the thyroid epithelium, causing a higher predisposition to malignant cell transformation.

Our study has several strengths, including the large number of TC case patients included, the availability of histological subtype and, in a subset of case patients, TNM stage, as well as lifestyle and anthropometric data. Conversely, lack of information on history of benign thyroid diseases, thyroidectomy among control subjects, and use of drugs that can interfere with the thyroid function represents the most important limitation of our study. We also did not have individual information on iodine deficiency, which is associated with...
increased risk of follicular TC (26). However, severe iodine deficiency is rare in EPIC countries. Past heavy exposure to ionizing radiation should not be a problem because individuals who reported a history of cancer other than nonmelanoma skin cancer were excluded.

Highly sensitive and specific assays were used, and case patients and control subjects were matched by year and time of blood collection and tested in the same batch. For each assay, the range of hormonal measurements among control subjects was consistent with the normal reference range provided by the manufacturer. The measurement of Tg, TSH, and thyroid hormones at only one point in time also has obvious limitations because nondifferential measurement error may lead to an underestimation of any real association. However, one measurement of TSH in serum has been reported to be representative of an individual’s exposure over 1 to 3 years (27). Moreover, TSH, Tg, and thyroid hormones were found to be stable over time when stored at least at −80°C.

Although our findings can inform on the etiology of TC, they do not support the use of either Tg or TSH level for screening or early detection of TC. Even for Tg, which performed better than TSH, the trade-off between sensitivity and specificity is too poor, notably in the light of the high prevalence of subclinical thyroid diseases and the aggressive treatment required, despite very good prognosis. Likewise, the American Thyroid Association recommends periodic measurement of Tg levels only in the follow-up of TC patients to monitor for residual or recurrent disease after thyroidectomy (28). The measurement of TSH is recommended in TC diagnosis to distinguish nonfunctional nodules from hyperfunctioning nodules, which are associated with TSH suppression and are rarely malignant (28).

In conclusion, our study does not support the involvement of TSH overstimulation in the etiology of TC, but it leaves to clinical trials the assessment of the indications for TSH suppressive treatment in TC patients. Improving the management of TC and subclinical thyroid diseases is a public health priority on account of the increasing frequency and cost of these conditions and the uncertainties over their biology (29).

References
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Notes
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