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Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study

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Other than the influence of ionizing radiation and benign thyroid disease, little is known about the risk factors for differentiated thyroid cancer (TC) which is an increasing common cancer worldwide. Consistent evidence shows that body mass is positively associated with TC risk. As excess weight is a state of chronic inflammation, we investigated the relationship between concentrations of leptin, adiponectin, C-reactive protein, interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF-α) and the risk of TC. A case-control study was nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study and included 475 first primary incident TC cases (399 women and 76 men) and 1,016 matched cancer-free cohort participants. Biomarkers were measured in serum samples using validated and highly sensitive commercially available immunoassays. Odds ratios (ORs) of TC by levels of each biomarker were estimated using conditional logistic regression models, adjusting for BMI and alcohol consumption. Adiponectin was inversely associated with TC risk among women (OR_{T3vs.T1} = 0.69, 95% CI: 0.49–0.98, \( P_{\text{trend}} = 0.04 \)) but not among men (OR_{T3vs.T1} = 1.36, 95% CI: 0.67–2.76, \( P_{\text{trend}} = 0.37 \)). Increasing levels of IL-10 were positively associated with TC risk in both genders and significantly so in women (OR_{T3vs.T1} = 1.59, 95% CI: 1.13–2.25, \( P_{\text{trend}} = 0.01 \)) but not in men (OR_{T3vs.T1} = 1.78, 95% CI: 0.80–3.98, \( P_{\text{trend}} = 0.17 \)). Leptin, CRP, IL-6 and TNF-α were not associated with TC risk in either gender. These results indicate a positive association of TC risk with IL-10 and a negative association with adiponectin that is probably restricted to women. Inflammation may play a role in TC in combination with or independently of excess weight.

What’s new?
How does being overweight lead to thyroid cancer? These authors investigated, using data from the EPIC cohort. Considering obesity as a state of chronic inflammation, they looked at levels of various proteins associated with inflammation, including C-reactive protein, IL-10, adiponectin, and others, and compared these with TC risk. Women with high adiponectin levels were less likely to develop thyroid cancer, while those with high IL-10 levels had increased TC risk. No significant association was seen in men.

Introduction
In Western countries, thyroid cancer incidence has been increasing over the last two decades thereby becoming the second most commonly diagnosed cancer after breast cancer in women younger than 45 years.\(^1,2\) The increase in the search of thyroid nodules mainly through ultrasonography has led to vast increases in differentiated thyroid cancers (TC), the most common form of thyroid cancer that includes papillary and follicular carcinomas.\(^3\) Exposure to ionizing radiations and history of benign thyroid diseases are the only
relatively strong risk factors for TC though unlikely the reason of the upward incidence trends.\textsuperscript{2–4} Other possible risk factors are ill-understood. There is consistent evidence that excess body weight and obesity are associated with a modest increase in risk of TC.\textsuperscript{5–7} and the mechanisms underlying this association may involve inflammation.\textsuperscript{8,9} Indeed, the adipose tissue of overweight individuals is characterized by the infiltration of macrophages resulting in chronic systemic inflammation and in the release of cytokines and adipokines into the circulation.\textsuperscript{10} Adipose tissue secretes hundreds of adipokines of which the best studied are leptin and adiponectin, which regulate important biological processes such as appetite, insulin sensitivity, thermogenesis, fatty acid oxidation and immune response.\textsuperscript{11} Adipokine secretion is altered in adipose tissue dysfunction and may contribute to a spectrum of obesity-associated diseases.\textsuperscript{9}

Both experimental and epidemiological data suggest that local organ-specific inflammation plays a role in TC and benign thyroid conditions. TC is often characterized by the infiltration of inflammation-immune cells, and autoimmune thyroid diseases, such as Hashimoto’s thyroiditis and Grave’s disease, have been associated, in some studies, with an increased risk of TC.\textsuperscript{12,13} Systemic inflammation, characterized by higher circulating levels of cytokines, has also been observed in patients with Graves’ disease, hyperthyroidism and toxic nodular goiter.\textsuperscript{14,15} Systemic inflammation has also been associated with the development of several cancer types and previous reports have shown that elevated levels of cytokines and low levels of adiponectin were associated with an increased risk of endometrial,\textsuperscript{16–18} breast,\textsuperscript{19} ovarian,\textsuperscript{20} liver\textsuperscript{21} and colon\textsuperscript{22} cancers.

Few retrospective case-control studies, mostly with very small sample size (including between 20 and 163 subjects), reported higher circulating levels of cytokines (including C-reactive protein [CRP], interleukin [IL]-6, IL-10, tumor necrosis factor [TNF]-\(\alpha\)) as well as leptin, among TC cases.\textsuperscript{23–27} Conversely, circulating levels of adiponectin, an adipokine that is inversely related to adiposity, were found to increase in risk of TC,\textsuperscript{12,13} and toxic nodular goiter.\textsuperscript{14,15} Systemic inflammation has also been associated with the development of several cancer types and previous reports have shown that elevated levels of cytokines and low levels of adiponectin were associated with an increased risk of endometrial, breast, ovarian, liver and colon cancers.\textsuperscript{22}

We have set up a study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to investigate the relationship between the risk of TC and the prediagnostic concentrations of leptin, adiponectin, CRP, IL-6, IL-10 and TNF-\(\alpha\). To our knowledge, this is the first prospective study investigating the association of prediagnostic levels of adipokines and inflammation markers with TC risk.

### Methods

#### Study population and blood sample collection

The EPIC cohort is a large, multicenter prospective study, designed to investigate the associations between nutritional, lifestyle, metabolic and genetic risk factors and cancer. It was initiated in 1992 in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom) and involved about 370,000 women and 150,000 men. Study population and baseline data collection have previously been described in details.\textsuperscript{29} In brief, questionnaires included data about diet, reproductive history, use of exogenous hormones, tobacco smoking and alcohol consumption, education level, occupational history, physical activity and history of selected diseases. Anthropometric variables were measured according to standardized protocols.\textsuperscript{29}

About 246,000 women and 140,000 men also provided a blood sample, collected according to a standardized protocol in France, Germany, Greece, Italy, the Netherlands, Norway, Spain and the United Kingdom.\textsuperscript{29} From each subject, about 30 ml of blood were drawn, and serum (except in Norway), plasma, erythrocytes and buffy coat were aliquoted in plastic straws of 0.5 ml each, which were stored in liquid nitrogen (\(-196^\circ\text{C}\)) in a centralized biobank. In Denmark, blood fractions were aliquoted into 1 ml tubes, and stored in the vapor phase of liquid nitrogen containers (\(-150^\circ\text{C}\)). In the Swedish center of Umea, blood samples were divided into 10 aliquots of 1.5 ml each (six plasma, two buffy coat and two erythrocytes), which were rapidly frozen at \(-80^\circ\text{C}\) in standard freezers.

All participants have given their consent to participate into the EPIC study. The Internal Review Board of IARC and local institutional review boards in participating centers have approved the study.

#### Follow-up for cancer incidence and vital status

Incident cancer cases were identified through record linkage with regional cancer registries in most countries and through health insurance records, cancer and pathology registries and active follow-up of study subjects in France, Germany and Greece. Data on vital status were obtained from mortality registries at the regional or national level, in combination with data collected by active follow-up (Greece). For each EPIC center, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status (dates varied between centers, from June 2008 to December 2013).

#### Selection of cases and controls

Case subjects were selected among participants who were cancer-free (other than nonmelanoma skin cancer), had donated blood at recruitment into the cohort and who were diagnosed with TC between recruitment and the end of follow-up. Cases were coded according to the 10th revision of the WHO International Classification of Disease (code C73). This analysis focused on differentiated thyroid cancer, i.e., papillary (morphologic codes: 8050, 8130, 8260, 8340–8344 and 8350), follicular carcinomas (8290, 8330–8335) and not otherwise specified, which are likely to also be papillary (8000, 8010, 8140). Thyroid cancer cases with rare or missing histological types (37 medullary, 9 anaplastic, 1 lymphoma, 4 other morphologies and 1 missing) were not included. A total
of 475 incident TC cases were included (363 papillary, 84 follicular and 28 not otherwise specified TC). Tumor-node-metastasis (TNM) stage was known for 56.4% of the eligible cases and used to group cancers into localized (T1) and more advanced (≥T2) cancers.

For each case subject with TC, two control subjects for women, and three for men were chosen at random among appropriate risk sets consisting of all cohort members who were alive and without a reported cancer diagnosis (except nonmelanoma skin cancer) at the time of diagnosis of the index case. Matching procedures have been described before. In brief, matching variables included study recruitment center, sex, age, date, time, fasting status at blood collection and duration of follow-up (duration for the control must be greater than for the index case). A total of 1,016 controls were selected for the study.

Laboratory measurements

Serum was used for laboratory assays except for samples from Norway (citrated plasma) and Umeå, Sweden (heparin plasma). Leptin was measured by immunoradiometric assay (IDS, Paris, France), while adiponectin and CRP were measured by enzyme-linked immunosorbent assays (R&D, United Kingdom). IL-6, IL-10 and TNF-α were measured by a highly sensitive multiplexing electrochemiluminescent method (V-PLEX™ Custom Human Cytokine Kit, Meso Scale Discovery, Rockville, MD).

All assays were performed at IARC by technicians who were blind to case-control status of the subjects. Samples from cases and matched controls were analyzed together, within the same analytical batch. For quality control, three plasma samples from nondiseased subjects were analyzed in duplicate within each analytical batch. Mean intrabatch coefficients of variation, calculated on the concentrations from the quality control samples, varied between 2.6% for CRP, to 9.9% for IL-10.

Of a total of 1,491 subjects, 5 had missing values for adiponectin, 6 for CRP, 37 for leptin and 49 for IL-6, IL-10 and TNF-α. These subjects were excluded from the analyses for each particular biomarker. Twenty-seven values (1.8%) were below the limit of quantification (LOQ) for CRP, 75 (5%) for IL-10 and 46 (3%) for IL-6. These values were set to the LOQ: 78 pg/ml for CRP, 0.15 pg/ml for IL-10 and 0.16 pg/ml for IL-6. No value was below the LOQ for leptin, adiponectin or TNF-α.

Statistical analyses

Participant characteristics (means or percentages) were compared between cases and controls within matched sets, for men and women separately, using conditional logistic regression. Concentrations of the biomarkers were transformed logarithmically to approximate the normal distribution in all parametric analyses.

Prediagnostic levels of inflammation markers among controls were compared between men and women, using Mann-Whitney-Wilcoxon test. Spearman’s partial correlation coefficients between inflammation markers and lifestyle factors were calculated among controls, adjusting for age at blood donation (continuous) and laboratory batch.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for TC in relation to sex-specific tertiles of inflammation markers (based on the distribution of controls) were estimated using logistic regression conditional on matching factors (basic models), separately for men and women. Tests for trends in ORs by tertiles were computed by assigning consecutive scores to the tertiles.

The effects of potential confounders (additionally to the matching criteria, controlled for by design) were examined by including additional terms into the logistic regression model. The following confounders were tested: smoking status, duration of smoking, physical activity, alcohol consumption, education level, age at menarche, parity, age at first FTP, number of FTP, breast feeding, menopausal status, exogenous hormone use, anthropometric variables (height, BMI, WC, HC and WHR). Only BMI and alcohol consumption affected point estimates by >10% and were therefore retained in the adjusted models.

For analyses of statistical heterogeneity by selected cofactors, p-values for heterogeneity were derived by testing an interaction term between the tertile score of inflammation markers and the cofactor.

All statistical tests and corresponding p-values were two-sided, and p-values <0.05 were considered statistically significant. All analyses were performed using the SAS software package (Version 9.4, SAS Institute, Cary, NC).

Results

Baseline characteristics of the study population are described in Table 1. Cases were diagnosed at a mean age of ~58 years, after an average follow-up time of about 8 years. Among women, TC cases were significantly taller, had a larger BMI and waist circumference and a lower alcohol intake than controls. The associations with height and alcohol intake but not BMI and waist circumference, were in the same direction in men as in women but no associations were significant, possibly due to the lower number of male than female cases.

Supporting Information Table 1 shows prediagnostic levels of inflammation markers in controls by gender. Levels of leptin and adiponectin were significantly higher while TNF-α levels were significantly lower in women than in men. Levels of CRP and other cytokines were similar in both genders.

Table 2 shows correlations between different inflammation markers, age and anthropometric indexes. The strongest correlations (≥0.49) were found between leptin and BMI and waist circumference in both genders. Adiponectin was moderately inversely correlated with BMI, waist circumference and leptin but positively correlated with age (~0.20). CRP, IL-6 and TNF-α were also moderately correlated with BMI, waist circumference and leptin and with each other. None of
the inflammation markers was substantially correlated with IL-10 or height.

Table 3 presents the association between tertiles of inflammation markers and TC risk, separately for women and men. Among women, a statistically significant inverse association was observed in the basic model between TC risk and adiponectin (OR_{T3vs.T1} = 0.67, 95% CI: 0.48–0.93, \( P_{\text{trend}} = 0.02\)) while IL-10 was positively associated (OR_{T3vs.T1} = 1.54, 95% CI: 1.10–2.16, \( P_{\text{trend}} = 0.02\)). Adjustment for TC risk factors did not substantially modify these findings (OR_{T3vs.T1} = 0.69,

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**Table 1. Selected characteristics of the study population at blood collection by gender**

|                           | Women Cases | Women Controls | Women p-value | Men Cases | Men Controls | Men p-value |
|---------------------------|-------------|----------------|--------------|-----------|--------------|-------------|
| Number                    | 399         | 791            | –            | 76        | 225          | –           |
| Age at blood collection (years)^2 | 50.2 (8.5)  | 50.2 (8.6)     | –            | 49.9 (8.9)| 49.8 (8.7)   | –           |
| Age at diagnosis (years)^2  | 58.4 (8.6)  | –              | –            | 58.5 (9.5)| –            | –           |
| Years between blood collection and cancer diagnosis^2 | 8.2 (4.4)    | –              | –            | 8.6 (4.7) | –            | –           |
| Height (cm)^2             | 161.3 (6.3) | 160.2 (6.6)    | 0.002        | 176.5 (6.7)| 175.3 (6.3)  | 0.14        |
| Body mass index (kg/m^2)^2 | 26.1 (4.5)  | 25.5 (4.6)     | 0.02         | 26.4 (3.0)| 26.4 (3.4)   | 0.87        |
| Waist circumference (cm)^2 | 81.9 (11.3) | 80.3 (11.1)    | 0.01         | 94.6 (10.0)| 94.5 (9.9)   | 0.95        |
| Alcohol intake (g/day)^2   | 6.1 (9.0)   | 7.5 (10.9)     | 0.02         | 17.5 (18.3)| 19.5 (23.6)  | 0.48        |

**Smoking status (%)^3**

- Never smoker: 60, 32
- Ex smoker: 21, 35
- Current smoker: 19, 33

**Education level (%)^3**

- None or primary: 42, 30
- Secondary or more: 58, 70

^1From logistic regression conditional on matching factors.

^2Mean and standard deviation.

^3Percentage excluding participants with missing variables.

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**Table 2. Spearman correlation coefficients between prediagnostic levels of inflammation markers^5 and age and anthropometric factors among controls and corresponding p-values^2 by gender**

|                  | Women          | Men            |
|------------------|----------------|----------------|
|                  | Age            | Alcohol intake | BMI  | Waist circ. | Height | Leptin | Adiponectin | CRP         | IL-10 | IL-6 |
| Leptin           | 0.11           | −0.12          | 0.64 | 0.59        | −0.10  |
| Adiponectin      | 0.21           | 0.13           | −0.18| −0.23       | 0.01   | −0.22  |
| CRP              | 0.17           | −0.07          | 0.41 | 0.39        | −0.08  | 0.36   | −0.17       |
| IL-10            | 0.01           | −0.02          | 0.08 | 0.07        | −0.04  | 0.07   | −0.01       | 0.13       |
| IL-6             | 0.15           | −0.13          | 0.37 | 0.33        | −0.12  | 0.25   | −0.10       | 0.36       | 0.26   |
| TNF-α            | 0.17           | −0.15          | 0.26 | 0.25        | −0.17  | 0.20   | −0.07       | 0.18       | 0.33   | 0.42 |

**CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.**

^4Adjusted for laboratory batch and age at blood donation (when appropriate).

^5p-Values <0.0001 in bold.
Table 3. Odds ratio (OR) of differentiated TC by inflammation marker tertile in women and men

| Inflammation Marker | Women | Men | P Interaction by Gender |
|---------------------|-------|-----|-------------------------|
|                     | Tertiles¹ | P_trend² | Tertiles¹ | P_trend² | P Interaction by Gender |
| Leptin (ng/ml)      | <15.6 | 15.6–29.1 | ≥29.1 | <7.6 | 7.6–11.6 | ≥11.6 | 0.79 |
| Cases/controls      | 113/250 | 147/250 | 128/249 | 26/73 | 25/73 | 24/72 |
| OR [95% CI]: basic model³ | 1.00 | 1.30 [0.95; 1.77] | 1.14 [0.81; 1.59] | 0.47 | 1.00 | 0.94 [0.50; 1.79] | 0.92 [0.47; 1.79] | 0.80 |
| Adiponectin (ng/ml) | <7,654.9 | 7,654.9–12,441.9 | ≥12,441.9 | <4,259.7 | 4,259.7–6257.8 | ≥6,257.8 | 0.07 |
| Cases/controls      | 155/262 | 130/262 | 111/261 | 23/75 | 23/75 | 30/75 |
| OR [95% CI]: basic model³ | 1.00 | 0.79 [0.58; 1.07] | 0.67 [0.48; 0.93] | 0.02 | 1.00 | 1.01 [0.51; 2.01] | 1.35 [0.67; 2.72] | 0.38 |
| C-reactive protein (ng/ml) | <722.1 | 722.1–1,887.8 | ≥1,887.8 | <754.7 | 754.7–2,055.5 | ≥2,055.5 | 0.34 |
| Cases/controls      | 135/262 | 121/261 | 140/261 | 28/75 | 29/75 | 19/74 |
| OR [95% CI]: basic model³ | 1.00 | 0.88 [0.65; 1.20] | 1.05 [0.77; 1.41] | 0.77 | 1.00 | 1.01 [0.54; 1.92] | 0.68 [0.35; 1.34] | 0.26 |
| IL-10 (pg/ml)       | <0.22 | 0.22–0.31 | ≥0.31 | <0.22 | 0.22–0.32 | ≥0.32 | 0.82 |
| Cases/controls      | 93/251 | 155/251 | 137/251 | 20/74 | 27/74 | 29/74 |
| OR [95% CI]: basic model³ | 1.00 | 1.69 [1.23; 2.32] | 1.54 [1.10; 2.16] | 0.02 | 1.00 | 1.61 [0.75; 3.46] | 1.81 [0.81; 4.02] | 0.17 |
Table 3. Odds ratio (OR) of differentiated TC by inflammation marker tertile in women and men (Continued)

| Tertiles | Women | Men | P interaction by gender |
|----------|-------|-----|-------------------------|
| OR [95% CI]: adj. model | OR [95% CI]: basic model | OR [95% CI]: adj. model | OR [95% CI]: adj. model |
| **IL-6 (pg/ml)** | **TNF-α (pg/ml)** |
| <0.34 | 0.34–0.53 | >=0.53 | <0.32 | 0.32–0.58 | >=0.58 | 0.31 |
| Cases/controls | 110/251 | 131/251 | 144/251 | 19/74 | 41/74 | 16/74 |
| OR | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| [95% CI] | 1.67 [1.21; 2.30] | 1.59 [1.13; 2.25] | 1.59 [0.74; 3.43] | 1.78 [0.80; 3.98] | 0.19 |
| OR | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| [95% CI] | 1.23 [0.89; 1.68] | 1.38 [0.99; 1.94] | 2.11 [1.10; 4.06] | 0.85 [0.39; 1.85] | 0.67 |
| OR | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| [95% CI] | 1.20 [0.87; 1.66] | 1.26 [0.88; 1.80] | 2.09 [1.09; 4.03] | 0.84 [0.39; 1.85] | 0.68 |
| OR | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| [95% CI] | 1.52–1.95 | 1.63–2.04 | 1.02 [0.53; 1.97] | 0.87 [0.41; 1.85] | 0.73 |
| Cases/controls | 125/252 | 121/251 | 138/251 | 26/74 | 27/74 | 23/74 |
| OR | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| [95% CI] | 0.95 [0.68; 1.32] | 1.08 [0.76; 1.53] | 1.01 [0.52; 1.95] | 0.86 [0.40; 1.84] | 0.71 |

1Tertiles based on the gender-specific distribution of controls.
2P trend values were computed by assigning consecutive scores (scores of 1–3) to the categories.
3Logistic regression conditional on matching factors.
4Logistic regression conditional on matching factors and adjusted for BMI, and alcohol consumption.
95% CI: 0.49–0.98, \( P_{trend} = 0.04 \) for adiponectin, and OR\(_T3vs.T1 = 1.59, 95\% \) CI: 1.13–2.25, \( P_{trend} = 0.01 \) for IL-10). None of the markers were significantly associated with TC risk among men (\( P_{trend} \geq 0.17 \)) but the positive association with IL-10 was similar to the one seen among women (OR\(_T3vs.T1 = 1.81, 95\% \) CI: 0.81–4.02 in the basic model; OR\(_T3vs.T1 = 1.78, 95\% \) CI: 0.80–3.98 in the adjusted model). Similar results were observed when analyses were restricted to papillary TC (Supporting Information Table 2). When genders were combined, the negative association with adiponectin was no longer significant (OR\(_T3vs.T1 = 0.79, 95\% \) CI: 0.58–1.07, \( P_{trend} = 0.13 \)), whereas a positive significant association with IL-10 was confirmed (OR\(_T3vs.T1 = 1.61, 95\% \) CI: 1.18–2.21, \( P_{trend} = 0.005 \)) (Supporting Information Table 3).

No statistically significant heterogeneity was observed in the inverse association between adiponectin and TC risk in women by age at blood collection, national TC incidence, education, smoking, BMI, waist circumference, menopausal status, histologic type, TNM stage (Fig. 1) and country (data not shown). The negative association with adiponectin was, however, absent among women in whom the interval between blood collection and TC diagnosis was <6 years (OR: 1.07, 95% CI: 0.81–1.43).

Finally, we explored the effect of adiponectin (middle and highest tertile vs. lowest tertile) according to BMI (<25 or \( \geq 25 \); data not shown). The OR was 0.96 (95% CI: 0.62–1.46) among normal-weight women and 0.66 (95% CI: 0.46–0.95) among overweight and obese women. Although, therefore, the negative association of high adiponectin level with TC
risk was only significant the heaviest women the 95% CI of the two ORs broadly overlap. Figure 2 (which includes both women and men) shows lack of significant heterogeneity in the positive association of TC risk with IL-10 by the same variables as in Figure 1 and country (data not shown).

**Discussion**

We showed for the first time in a prospective study that high adiponectin levels were associated with a lower risk of TC among women while elevated IL-10 levels were associated with an increased risk of TC probably in both genders. Lep- tin, CRP, IL-6 and TNF-alpha were not associated with TC risk in either gender.

Our results on adiponectin are consistent with the inverse association observed with papillary TC in a previous case-control study. Although Mitsiades et al.

Figure 2. Odds ratios of differentiated TC for an increase in one tertile of IL-10, stratified by selected variables.

| Gender            | Cases/ Controls | OR^1 | 95%CI          |
|-------------------|-----------------|------|---------------|
| Female            | 385/753         | 1.24 | 1.05-1.47     |
| Male              | 70/222          | 1.30 | 0.90-1.92     |
| Age at blood collection |                |      |               |
| < 56.5 years     | 154/333         | 1.10 | 0.86-1.43     |
| 46.5-56.5 years  | 151/318         | 1.22 | 0.93-1.61     |
| ≥ 56.5 years     | 150/324         | 1.46 | 1.12-1.92     |
| Thyroid cancer incidence |            |      |               |
| High              | 281/944         | 1.32 | 1.08-1.62     |
| Low               | 180/383         | 1.14 | 0.90-1.45     |
| Education         |                |      |               |
| Primary school    | 177/372         | 1.32 | 1.03-1.70     |
| Secondary or more | 270/596         | 1.22 | 1.06-1.48     |
| Smoking           |                |      |               |
| Never             | 554/532         | 1.21 | 0.90-1.51     |
| Ever              | 200/428         | 1.34 | 1.07-1.68     |
| BMI kg/m2         |                |      |               |
| < 25              | 202/477         | 1.22 | 0.99-1.51     |
| ≥ 25              | 239/498         | 1.27 | 1.03-1.57     |
| Waist circumference, cm |         |      |               |
| < 82              | 232/520         | 1.19 | 0.97-1.45     |
| ≥ 82              | 229/425         | 1.36 | 1.08-1.71     |
| Histological type |                |      |               |
| Papillary         | 355/947         | 1.31 | 1.10-1.57     |
| Follicular        | 90/168          | 1.05 | 0.73-1.49     |
| TNM stage         |                |      |               |
| T1                | 154/320         | 1.14 | 0.87-1.51     |
| More advanced     | 105/224         | 1.35 | 0.98-1.85     |
| Follow-up time    |                |      |               |
| < 6 years         | 151/318         | 1.52 | 1.16-2.01     |
| ≥ 6-10 years      | 136/281         | 1.30 | 0.83-1.85     |
| ≥ 10 years        | 170/376         | 1.16 | 0.90-1.50     |
| Total             | 461/975         | 1.25 | 1.07-1.46     |

^1 logistic regression conditional on matching factors and adjusted for BMI and alcohol consumption.

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The main strength of our study includes its large sample size and its prospective design. As circulating levels of inflammation markers might be affected by the presence of the tumor, as well by diagnostic and therapeutic procedures, pre-diagnostic concentrations are essential when examining the etiologic role of inflammation in TC development to avoid reverse causation bias. Our study has also limitations, particularly the fact that we only measured inflammation markers at one point in time. However, most inflammation markers have shown good reproducibility in samples collected at different time points. Repeated measurements of inflammation markers and/or anthropometry and more in-depth assessment of fat distribution would nevertheless improve the classification of individuals and therefore lead to stronger associations with TC risk. The limited sample size in men that reflects however the epidemiology of TC limit the interpretation of the results in this group. In addition, although information was available on histological subtypes of TC, EPIC data did not include history of benign thyroid diseases, thyroidectomy among control subjects and use of drugs that could interfere with thyroid function. Likewise, individual information on iodine deficiency and past exposure to ionizing radiations have not been collected but we know that severe iodine deficiency is rare in EPIC countries and that exposure to ionizing radiation due to previous cancer treatment is unlikely because we excluded prevalent cancer cases other than nonmelanoma skin cancers. Finally, as the increase in incidence observed over the last decades in differentiated thyroid carcinomas is largely driven by changes in diagnostic practices, an additional limitation is that we do not have any indication on how the cancers have been diagnosed.

In conclusion, our results suggest a possible negative association of TC risk with prediagnostic circulating levels of adiponectin in women and an overall positive association with those of IL-10. Longer follow-up in EPIC or the combination of EPIC data with additional cohort studies are necessary to understand whether adiponectin and, possibly, other inflammation markers play a role in TC risk in combination with or independently of excess weight.

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