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Circulating endogenous sex steroids and risk of differentiated thyroid carcinoma in men and women

Sabina Rinaldi[1] | Laure Dossus[1] | Pekka Keski-Rahkonen[1] | Agneta Kiss[1] | Anne-Sophie Navionis[1] | Carine Biessy[1] | Ruth Travis[2] | Elisabete Weiderpass[1] | Isabelle Romieu[3] | Anne Kirstine Eriksen[4] | Anne Tjonneland[4,5] | Marina Kvaskoff[6] | Marianne Canonico[6] | Thérèse Truong[6] | Verena Katzke[7] | Rudolf Kaaks[7] | Alberto Catalano[8] | Salvatore Panico[9] | Giovanna Masala[10] | Rosario Tumino[11] | Marko Lukic[12] | Karina Standahl Olsen[12] | Raul Zamora-Ros[13] | Carmen Santiuste[14,15] | Amaia Aizpurua Atxega[16,17] | Marcela Guevara[15,18,19] | Miguel Rodriguez-Barranco[15,20,21] | Maria Sandstrom[22] | Joakim Hennings[23] | Martin Almquist[24,25] | Elom Aglago Kouassivi[26] | Sofia Christakoudi[26,27] | Marc Gunter[1] | Silvia Franceschi[28]

Correspondence
Sabina Rinaldi, International Agency for Research on Cancer, 25 Avenue Tony Garnier, CS 90627, 69366 Lyon cedex 07, France.
Email: rinaldis@iarc.who.int

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Abstract

Thyroid cancer (TC) is substantially more common in women than in men, pointing to a possible role of sex steroid hormones. We investigated the association between circulating sex steroid hormones, sex hormone binding globulin (SHBG) and the risk of differentiated TC in men and women within the European Prospective Investigation into Cancer and nutrition (EPIC) cohort. During follow-up, we identified 333 first primary incident cases of differentiated TC (152 in pre/peri-menopausal women, 111 in post-menopausal women, and 70 in men) and 706 cancer-free controls. Women taking exogenous hormones at blood donation were excluded. Plasma concentrations of testosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone and progesterone (in pre-menopausal women only) were performed using liquid chromatography/mass spectrometry method. SHBG concentrations were measured by immunoassay. Odds ratios (ORs) were estimated using conditional logistic regression models adjusted for possible confounders. No significant associations were observed in men and postmenopausal women, while a borderline significant increase in differentiated TC risk was observed with increasing testosterone (adjusted OR T3 vs T1:

Abbreviations: APCI, atmospheric pressure chemical ionization; BMI, body mass index; CIs, confidence intervals; DHEA, dehydroepiandrosterone; EPIC, European Prospective Investigation into Cancer and nutrition; LC/MS, liquid chromatography/mass spectrometry; LC-HRMS, liquid chromatography-high resolution mass spectrometry; LLOQs, lower limits of quantification; MS/MS, tandem mass spectrometry; NA, not applicable; OC, oral contraceptive; ORs, odds ratios; P2/E2, ratio progesterone/estradiol; SHBG, sex hormone binding globulin; TC, thyroid cancer; TNM, tumor-node-metastasis.

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1.68, 95% CI: 0.96–2.92, $p_{trend} = .06$) and androstenedione concentrations in pre/perimenopausal women (adjusted OR T3 vs T1: 1.78, 95% CI: 0.96–3.30, $p_{trend} = .06$, respectively). A borderline decrease in risk was observed for the highest progesterone/estradiol ratio (adjusted OR T3 vs T1: 0.54, 95% CI: 0.28–1.05, $p_{trend} = .07$). Overall, our results do not support a major role of circulating sex steroids in the etiology of differentiated TC in post-menopausal women and men but may suggest an involvement of altered sex steroid production in pre-menopausal women.

KEYWORDS
differentiated thyroid cancer, prospective study, sex steroids

What's new?

Thyroid cancer occurs more often in women than men, suggesting that sex hormones may contribute to the disease. Here, the authors investigated the association between circulating sex steroid hormones, sex hormone binding globulin protein (SHBG), and the risk of thyroid cancer in both men and women using data from the European Prospective Investigation into Cancer and nutrition (EPIC). They measured concentrations of testosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone and progesterone (in pre-menopausal women only), as well as SHBG. Overall, they did not detect a strong association between hormones, SHBG and thyroid cancer incidence.

1 | INTRODUCTION

Thyroid cancer (TC) is the most common endocrine cancer and has become one of the most frequent cancers in women worldwide.[1] TC originates from follicular thyroid cells and is classified into two main histological groups: the much more frequent differentiated TC (mainly the papillary, followed by the follicular type) and undifferentiated TC.[2] The only well-established risk factors for differentiated TC are exposure to ionizing radiation and history of benign thyroid nodules and goiter.[3–5] However, evidence is accumulating that obesity and body fat are also weakly but consistently associated with TC risk.[6]

TC incidence is about three times higher in women than in men in almost all countries (ratio approximately 3:1)[1] and the incidence of the disease is highest during women's reproductive years[2] pointing to a possible role of sex steroid hormones.[7–9] The increased TC risk observed with obesity[10] (a status associated with insulin resistance, increased growth factor and sex steroid concentrations) and history of breast cancer[11] may lend additional support to the hypothesis of an involvement of sex hormones, particularly estrogen levels.

Results from a few in vitro studies suggested that exposure of TC cells to estradiol increases cell proliferation,[12] while exposure to tamoxifen decreases it.[13] In addition, estrogen, progesterone and androgen receptors are expressed in both thyroid tumors and in normal thyroid tissues, although at low concentrations.[14–17]

Here, we report the results of the first prospective study conducted on circulating sex steroid hormones, sex hormone binding globulin (SHBG) and risk of differentiated TC in men and women. The study is nested within a large, multicentric cohort, the European Prospective Investigation into Cancer and nutrition (EPIC)study.

2 | MATERIALS AND METHODS

2.1 | Study population and blood sample collection

The EPIC cohort is a large, multi-center prospective study, established to investigate the associations between nutritional, lifestyle and metabolic risk factors with cancer risk. The study began in 1992 and over 520,000 subjects (about 370,000 women and 150,000 men) were recruited in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the UK). Study population, data and biological sample collection have been previously described in detail.[18] About 246,000 women and 140,000 men also provided a blood sample, collected according to standardized protocols.[19]

2.2 | Follow-up for cancer incidence and vital status

Incident cancer cases were identified through different methods, including linkage with regional cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom), health insurance records, cancer and pathology registries and active follow-up of study subjects (France, Germany and 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).

2.3 | Assessment of menopausal status and phase of menstrual cycle at blood collection in women

Women were considered premenopausal if they reported menstrual periods over the past 12 months before recruitment, or when they were below the age of 42 years and had either a hysterectomy or missing information on menopausal status. Data to assess a woman's phase of cycle were collected,[20] and was defined as follows: "early follicular" (days 0–7 of the cycle), "late follicular" (days 8–11), "periovulatory" (days 12–16), "midluteal" (days 20–24) and "other luteal" (days 17–19 or days 25–40). Women were considered as postmenopausal when they reported any of the following: (i) no menses over the past 12 months before recruitment; (ii) bilateral ovariectomy or (iii) either a hysterectomy or missing information on menopausal status at age 55 years or above. Other women were considered as perimenopausal/unknown menopause status, and are referred to as perimenopausal throughout the article.

2.4 | Selection of cases and controls

In this study, we included cases and controls from EPIC centers located in France, Italy, Spain, the United Kingdom, The Netherlands, Denmark, Sweden, Norway and Germany. Eligible subjects were selected among participants without any previous cancers (except non-melanoma skin cancer) and had provided blood samples. For women, the study subjects (case and control subjects) were selected among women who reported no use of exogenous hormones at blood donation. Cases had a diagnosis of differentiated TC according to the 10th revision of the WHO International Classification of Disease (code C73), that is, papillary (morphologic codes: 8050, 8130, 8260, 8340–8344 and 8350), follicular carcinomas (8290, 8330–8335), and not otherwise specified TC (8000, 8010, 8140), which are likely to also be papillary TC. Thyroid cancer cases with rare or missing histological types (37 medullary, nine anaplastic, one lymphoma, four other morphologies and one missing) were excluded from the study. In women, 116 cases taking exogenous steroid hormones at blood donation were identified and excluded from the study. A total of 333 incident TC cases were selected (250 papillary, 61 follicular and 22 not otherwise specified TC) of which 70 in men. Tumor-node-metastasis (TNM) stage was known for 58% 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 control subjects for men were chosen at random among appropriate risk sets consisting of all eligible cohort members. An incidence density sampling protocol for control selection was used, such that controls could include subjects who became cases later in time, and each control subject could also be sampled more than once. Matching characteristics for cases and controls included study recruitment center; sex; age (±1 year); date (±3 months); time (±1 h); fasting status (<3 h, 3–6 h, >6 h) at blood collection, and duration of follow-up. In women, menopausal status (pre-, post- and perimenopausal status) and phase of menstrual cycle in premenopausal women ('follicular'—merging early and late follicular phases, 'periovulatory', 'luteal'—merging mid and other-luteal phases; missing) were additional matching criteria.

2.5 | Laboratory analyses

Citrated plasma was used for laboratory assays except for samples from Umeå, Sweden where heparin plasma was used. All assays were performed by the laboratory personnel of the Nutrition and Metabolism Branch at IARC, who were blinded as to the case–control status of the study subjects. Samples from cases and matched controls were measured in the same analytical batch. Sex steroids (androstenedione, testosterone, dehydroepiandrosterone—DHEA, estrone, estradiol and progesterone) were measured on a high-resolution platform (LC-HRMS) consisting of a high-performance chromatography system and a high-resolution mass spectrometer (Ultimate 3000, Q Exactive; Thermo Scientific). In brief, the plasma/serum sample preparation was based on liquid–liquid extraction using methyl tert-butyl ether. The organic extract was dried and then derivatized with 1,2-dimethylimidazole-5-sulfonyl chloride according to a well-defined protocol[21] and injected onto the reversed phase chromatographic column. The analytes were ionized in positive polarity using an atmospheric pressure chemical ionization (APCI) source and detected by monitoring analyte-specific MS/MS transitions. Lower limits of quantification (LLOQs) were as follows: estradiol: 1.5 pg/ml; estrone 2.5 pg/ml; androstenedione, testosterone and progesterone: 15 pg/ml; DHEA: 250 pg/ml. Progesterone was quantified only in pre- and perimenopausal women. SHBG concentrations were measured using a commercially available immunoradiometric assay (by Cis-Bio, Eurobio, Courtaboeuf, France).

No concentrations below the LLOQs were observed, and only one sample was above the upper limit of quantification for estradiol (1750 pg/ml), and the concentration was set to that level. Intra-batch and inter-batch coefficients of variation (based on duplicate quality control samples added in each batch of analyses) ranged from 2.9% for estradiol to 10.2% for progesterone, and from 3% for testosterone to 20.2% for DHEA, respectively.

Plasma concentrations of free testosterone and free estradiol, unbound to SHBG or albumin, were calculated from the absolute concentrations of each of the steroids and SHBG using validated mass action equations, and assuming a constant serum albumin concentration of 43 g/L.[22]

2.6 | 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 and were compared between cases and controls in women and men, separately, by using a Wilcoxon pairwise rank test.

Non-parametric Spearman's partial correlation coefficients between biomarkers and lifestyle factors were calculated among controls, in men, and pre/peri and post-menopausal women separately, adjusting for age at blood donation (continuous) and laboratory batch of analyses.

As progesterone, estrone and estradiol showed systematic variations over the estimated phases of the menstrual cycle, we used spline regression methods to model these variations during the menstrual cycle for cases and controls combined. We then calculated residuals of the spline regression models to describe how the hormone levels deviated from predicted values.[20] In this way, cut points for different categories of concentrations of estradiol and progesterone were standardized throughout the phases of the menstrual cycle. The progesterone/estradiol ratio was calculated as the ratio of hormone concentrations in their respective units of measures (nmol/l and pmol/l, respectively).

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for differentiated TC in relation to tertiles of sex hormones and SHBG concentrations were estimated using conditional logistic regression analyses, separately for men, pre/peri, and postmenopausal women. Cut-off points for tertiles were based on the distribution of the controls. Tests for trends in ORs by tertile were computed by assigning consecutive scores (scores of 1, 2, 3) to the tertiles. Continuous linear associations were calculated on log2 transformed variables and corresponding ORs were computed for a doubling of the biomarker level.

The effects of potential additional confounders (additional to the matching criteria) were examined by including additional terms into the logistic regression models. The following confounders were tested: height (continuous), body mass index (BMI) (continuous), waist circumference (continuous), waist-to-hip ratio (continuous), smoking status (Never, Former, Smoker, Unknown), duration of smoking (<5; [5–10]; [10–20]; ≥20 years; missing), total physical activity (Inactive, Moderately inactive, Moderately active, Active, Missing), alcohol consumption (continuous), education level (None/Primary school completed; Technical/professional or secondary school; longer education [incl. University deg.]; Not specified/missing). Among women, also age at menarche (continuous), parity, full term pregnancy (yes/no), age at first full term pregnancies (<20; [20–25]; [25–30]; 30+ years old, missing), number of full term pregnancies (continuous and in categories: 0; 1; 2; 3+; missing), breast feeding (ever vs never), and, exogenous hormone use (ever vs never) were considered among possible confounders. For covariate data, a missing category was used for categorical variables, while for continuous variables (waist circumference and alcohol), sex-specific median values were imputed. Only height, waist circumference, alcohol intake, smoking status, education level and physical activity affected point estimates by more than 10% and were therefore retained in the final models. In women, analyses were stratified by menopausal status (pre/peri and post).

For analyses of statistical heterogeneity by selected cofactors (small localized tumors T1 vs larger sizes and protrusion into adjacent tissues), papillary vs follicular, country, age at diagnosis (<50 years), time to follow-up (median, <5 years between blood donation and diagnosis, vs more than 5 years), p values for heterogeneity were computed by testing an interaction term between the tertile score of the biomarkers and the cofactor.

All statistical tests and corresponding p values were two-sided, and p values <.05 were considered statistically significant. All analyses were performed using the SAS software package (Version 9.4, SAS Institute, Cary, NC).

3 | RESULTS

Median age at blood donation was 44 years in pre/perimenopausal women, 58 years in post-menopausal women, and 51 years in men (Table 1). Cancer occurred on average 9 years after blood donation. Compared to controls, cases in pre/perimenopausal women had a higher BMI, larger waist circumference, and drank less alcohol, while no significant differences could be observed between cases and controls in postmenopausal women, nor in men. No significant differences in prediagnostic levels of sex steroids and SHBG were observed between cases and controls in post nor pre/peri-menopausal women, nor in men.

After adjustment for laboratory batch and age in control subjects, the strongest correlations (>0.30 in either direction) were found, as expected, between free and total fractions of sex hormones and between steroids and SHBG concentrations (Table S1). Among both pre/perimenopausal and postmenopausal women, SHBG was negatively associated with BMI and waist circumference. BMI and waist circumference were positively associated with free estradiol only in postmenopausal women and in men. DHEA and estrone were negatively and positively associated with age in men respectively.

Table 2 shows the relationship between differentiated TC and the concentration of sex hormones and SHBG in pre/peri-menopausal women. An increase in differentiated TC risk was observed with the increase of testosterone (fully adjusted OR_{T3vsT1}: 1.68, 95% CI: 0.96–2.92, $p_{trend} = 0.06$) and androstenedione concentration (OR_{T3vsT1}: 1.78, 95% CI: 0.96–3.30, $p_{trend} = 0.06$, respectively). A significant decrease in risk was observed with the progesterone/estradiol ratio in the crude analysis (OR_{T3vsT1}: 0.51, 95% CI: 0.28–0.93, $p_{trend} = 0.03$) but the association lost statistical significance in the fully adjusted models (adjusted OR_{T3vsT1}: 0.54, 95% CI: 0.28–1.05, $p_{trend} = 0.07$). A decreased risk was observed for SHBG in the crude analyses (OR_{T3vsT1}: 0.65, 95% CI: 0.40–1.05, $p_{trend} = 0.06$).

Results were similar when analyses were restricted to premenopausal women only, or when residuals were used for estrone, estradiol and progesterone analyses instead of their absolute concentrations (results not shown). When analyses were stratified by cancer subtype (follicular vs papillary), by tumor size (T1 vs larger sizes), by country, by age at diagnosis (<50 years old), and by time to follow-up (<5 years between blood donation and diagnosis, vs more than 5 years), no significant heterogeneity was found, but subgroup analyses had limited statistical power (data not shown).

Figure 1 shows the relationship between sex hormone and SHBG concentrations, and the risk of differentiated TC in post-menopausal women and in men, when comparing highest vs lower tertiles (T3 vs

TABLE 1 Selected characteristics of the study population, separately for cases and matched controls, in men, and pre/peri and post-menopausal women.

	Women					
	Pre/perimenopause		Post-menopause		Men	
	Cases	Controls	Cases	Controls	Cases	Controls
Number	152	288	111	210	70	208
Age at blood collection (years)[a]	44.8 (37.4–51.3)	44.0 (37.0–51.3)	57.7 (52.2–64.7)	58.1 (52.4–65.0)	51.0 (40.0–60.9)	51.2 (40.2–60.9)
Age at diagnosis (years)[a]	53.5 (44.9–62.3)	-	66.2 (58.5–75.5)	-	59.4 (46.8–71.5)	-
Height (cm)[a]	161.0 (152.5–170.0)	160.9 (152.0–168.0)	160.0 (152.0–168.0)	159.6 (151.0–168.0)	176.0 (167.9–185.0)	175.5 (168.0–183.0)
Body mass index (kg/m^2)[a]	25.7 (21.7–32.4)	24.4 (20.5–31.2)	25.7 (21.1–32.0)	25.5 (21.5–32.0)	26.0 (22.6–29.8)	25.9 (22.3–30.5)
Waist circumference (cm)[a]	79.6 (70.0–96.5)	76.8 (66.3–93.0)	80.0 (68.0–97.0)	80.1 (70.0–96.0)	94.0 (82.0–107.0)	93.0 (82.0–106.0)
Alcohol at recruitment (g/d)[a]	1.3 (0.0–16.6)	3.6 (0.0–24.6)	1.9 (0.0–20.9)	1.7 (0.0–22.9)	11.5 (0.7–44.1)	13.0 (0.6–49.1)
Physical activity (%)[b]						
Inactive	21 (13.9)	48 (16.8)	6 (5.5)	30 (14.6)	12 (19.1)	48 (25.7)
Moderately inactive	41 (27.1)	77 (27.0)	38 (34.9)	71 (34.6)	28 (44.4)	53 (28.3)
Moderately active	70 (46.4)	143 (50.2)	58 (53.2)	91 (44.4)	61 (22.2)	61 (32.6)
Active	19(12.6)	17 (6.0)	7 (6.4)	13 (6.4)	9 (14.3)	25 (13.4)
Smoking status (%)[b]						
Never	93 (62.0)	163 (56.6)	69 (62.2)	139 (66.5)	21 (30.9)	75 (36.2)
Former	32 (21.3)	64 (22.2)	20 (18.0)	39 (18.7)	26 (38.2)	77 (37.2)
Current	25 (16.7)	61 (21.2)	22 (19.8)	31 (14.8)	21 (30.9)	55 (26.6)
Educational level (%)[b]						
None or primary	67 (45.0)	125 (43.6)	61 (56.5)	101 (49.0)	24 (35.8)	67 (32.4)
Secondary or more	82 (55.0)	162 (56.4)	47 (43.5)	105 (51.0)	43 (64.2)	140 (67.6)
Biomarkers[c]						
Testosterone (nmol/l)[a]	0.6 (0.3–1.1)	0.6 (0.3–1.0)	0.5 (0.3–0.9)	0.5 (0.3–1.0)	11.9 (8.2–16.9)	12.8 (8.3–18.4)
Free testosterone (pmol/l)[a]	9.4 (4.4–16.7)	8.6 (4.8–15.2)	7.2 (3.7–14.1)	7.3 (4.2–15.6)	250.8 (180.0–341.2)	250.6 (174.8–359.4)
Androstenedione (nmol/l)[a]	2.7 (1.4–4.5)	2.6 (1.5–4.4)	1.6 (0.8–2.8)	1.4 (0.8–2.8)	2.4 (1.5–4.2)	2.4 (1.5–3.7)
DHEA (nmol/l)[a]	9.2 (4.1–19.1)	9.2 (4.3–17.5)	5.7 (2.1–10.0)	5.3 (1.8–12.2)	6.1 (3.1–15.8)	6.9 (3.3–13.6)
Estrone (pmol/l)[a]	207.6 (76.6–440.7)	186.4 (69.0–452.9)	76.0 (36.4–179.2)	72.8 (42.0–145.5)	109.8 (72.3–175.8)	106.4 (67.6–175.7)
Estradiol (pmol/l)[a]	248.6 (14.8–576.0)	236.6 (21.3–631.4)	14.5 (2.8–38.3)	14.1 (7.1–36.2)	65.8 (42.7–99.8)	69.0 (38.4–109.5)
Free estradiol (pmol/l)[a]	5.8 (0.4–14.7)	5.5 (0.6–14.8)	0.3 (0.1–1.1)	0.4 (0.2–0.9)	1.8 (1.0–3.0)	1.8 (1.1–3.1)
Progesterone (nmol/l)[a]	0.7 (0.1–31.1)	1.0 (0.1–29.0)	-	-	-	-
Ratio P/E2[a]	0.0074 (0.0006–0.0781)	0.0105 (0.0006–0.0853)	-	-	-	-
SHBG (nmol/l)[a]	40.7 (21.6–89.4)	46.1 (23.3–82.7)	43.3 (20.3–86.7)	40.0 (20.4–82.9)	26.1 (14.4–43.3)	27.6 (15.1–52.4)

[a]Median (10–90 percentile).

[b]Percentage excluding participants with missing variables (n = 39 for physical activity, six for smoking status and 15 for educational level).

[c]Missing values: 5 for sex-hormone binding globulin (SHBG), 13 for Testosterone, 14 for Free Testosterone, 13 for Androstenedione; 13 for dehydroepiandrosterone (DHEA), 14 for Estrone, 20 for Estradiol, 21 for Free Estradiol and 14 for Progesterone (9 pre, 5 peri-menopausal women).

TABLE 2 Risk (odds ratio, OR [95% confidence interval, CI]) of differentiated thyroid cancer by categories of sex steroids and SHBG in pre/peri menopausal women.

	Pre/peri menopausal women					
	Tertiles			p_{trend}[a]	*Continous*[b]	p_{trend}[c]
Testosterone (nmol/l)	*<0.53*	*0.53–0.76*	*≥0.76*			
Cases/Controls	47/95	45/95	59/94		*151/284*	
Crude[d]	1.00	0.99 (0.58–1.61)	1.29 (0.79–2.12)	0.30	*1.09 (0.80–1.48)*	*0.59*
Further adj. by waist	1.00	1.00 (0.60–1.69)	1.37 (0.83–2.29)	0.21	*1.13 (0.83–1.55)*	*0.43*
Fully adjusted model[e]	1.00	1.07 (0.61–1.86)	1.68 (0.96–2.92)	**0.06**	*1.24 (0.88–1.74)*	*0.22*
Free testosterone (pmol/l)	*<7.26*	*7.26–10.36*	*≥10.36*			
Cases/Controls	46/95	41/95	64/94		*151/284*	
Crude[d]	1.00	0.87 (0.50–1.49)	1.44 (0.88–2.36)	0.13	*1.16 (0.88–1.54)*	*0.28*
Further adj. by waist	1.00	0.76 (0.44–1.33)	1.14 (0.68–1.91)	0.58	*1.02 (0.76–1.37)*	*0.87*
Fully adjusted model[e]	1.00	0.78 (0.43–1.40)	1.30 (0.75–2.26)	0.33	*1.07 (0.79–1.45)*	*0.66*
Androstenedione (nmol/l)	*<2.18*	*2.18–3.05*	*≥3.05*			
Cases/Controls	47/95	45/95	59/94		*151/284*	
Crude[d]	1.00	1.04 (0.61–1.77)	1.40 (0.81–2.42)	0.21	*1.18 (0.82–1.69)*	*0.39*
Further adj. by waist	1.00	1.03 (0.60–1.76)	1.39 (0.80–2.44)	0.23	*1.19 (0.82–1.73)*	*0.35*
Fully adjusted model[e]	1.00	1.17 (0.66–2.07)	1.78 (0.96–3.30)	**0.06**	*1.43 (0.95–2.17)*	*0.09*
DHEA (nmol/l)	*<7.21*	*7.21–11.93*	*≥11.93*			
Cases/Controls	53/95	50/95	48/94		*151/284*	
Crude[d]	1.00	1.00 (0.60–1.66)	0.95 (0.56–1.61)	0.84	*1.06 (0.83–1.35)*	*0.64*
Further adj. by waist	1.00	0.99 (0.59–1.67)	0.95 (0.55–1.64)	0.85	*1.08 (0.84–1.38)*	*0.56*
Fully adjusted model[e]	1.00	1.11 (0.63–1.96)	1.07 (0.60–1.89)	0.83	*1.11 (0.86–1.44)*	*0.43*
Estrone (pmol/l)	*<146.5*	*146.5–273.4*	*≥273.4*			
Cases/Controls	47/95	56/95	48/94		*151/284*	
Crude[d]	1.00	1.22 (0.69–2.15)	1.04 (0.58–1.88)	0.98	*1.04 (0.82–1.31)*	*0.75*
Further adj. by waist	1.00	1.17 (0.66–2.10)	0.99 (0.54–1.81)	0.89	*1.02 (0.81–1.29)*	*0.86*
Fully adjusted model[e]	1.00	1.32 (0.71–2.43)	1.04 (0.55–1.95)	0.94	*1.04 (0.81–1.33)*	*0.74*
Estradiol (pmol/l)	*<148.1*	*148.1–362.7*	*≥362.7*			
Cases/Controls	51/95	50/95	50/94		*151/284*	
Crude[d]	1.00	0.94 (0.54–1.65)	0.95 (0.55–1.66)	0.89	*1.01 (0.87–1.16)*	*0.91*
Further adj. by waist	1.00	0.95 (0.53–1.70)	1.07 (0.60–1.89)	0.78	*1.03 (0.89–1.19)*	*0.73*
Fully adjusted model[e]	1.00	1.01 (0.54–1.87)	1.12 (0.61–2.05)	0.69	*1.04 (0.89–1.20)*	*0.65*
Free estradiol (pmol/l)	*<3.54*	*3.54–8.42*	*≥8.42*			
Cases/Controls	49/95	48/95	54/94		*151/284*	
Crude[d]	1.00	0.99 (0.55–1.78)	1.11 (0.62–2.00)	0.69	*1.02 (0.88–1.17)*	*0.81*
Further adj. by waist	1.00	1.01 (0.55–1.84)	1.10 (0.61–1.99)	0.73	*1.01 (0.87–1.17)*	*0.88*
Fully adjusted model[e]	1.00	1.12 (0.59–2.11)	1.18 (0.63–2.22)	0.55	*1.02 (0.87–1.18)*	*0.82*
Progesterone (nmol/l)	*<0.31*	*0.31–7.03*	*≥7.03*			
Cases/Controls	55/91	50/91	40/90		*145/272*	
Crude[d]	1.00	0.81 (0.48–1.36)	0.56 (0.29–1.11)	0.10	*0.93 (0.84–1.02)*	*0.12*
Further adj. by waist	1.00	0.93 (0.54–1.58)	0.63 (0.32–1.26)	0.21	*0.94 (0.85–1.03)*	*0.19*
Fully adjusted model[e]	1.00	1.02 (0.58–1.80)	0.63 (0.30–1.32)	0.25	*0.95 (0.86–1.06)*	*0.37*
Progesterone/Estradiol ratio	*<0.004*	*0.004–0.04*	*≥0.04*			
Cases/Controls	62/91	45/91	38/90		*145/272*	
Crude[d]	1.00	0.70 (0.42–1.15)	0.51 (0.28–0.93)	**0.03**	*0.92 (0.84–1.01)*	***0.07***
Further adj. by waist	1.00	0.70 (0.42–1.17)	0.53 (0.28–0.98)	**0.04**	*0.92 (0.84–1.01)*	***0.08***

TABLE 2 (Continued)

	Pre/peri menopausal women					
	Tertiles			p_{trend}[a]	*Continous*[b]	p_{trend}[c]
Fully adjusted model[e]	1.00	0.76 (0.44–1.29)	0.54 (0.28–1.05)	**0.07**	*0.93 (0.84–1.02)*	*0.14*
SHBG (nmol/l)	*<37.45*	*37.45–55.44*	*≥55.44*			
Cases/Controls	69/96	38/96	45/96		*152/288*	
Crude[d]	1.00	0.57 (0.35–0.94)	0.65 (0.40–1.05)	**0.06**	*0.88 (0.68–1.14)*	*0.34*
Further adj. by waist	1.00	0.69 (0.42–1.15)	0.95 (0.55–1.63)	0.75	*1.16 (0.86–1.58)*	*0.33*
Fully adjusted model[e]	1.00	0.75 (0.44–1.28)	1.00 (0.55–1.82)	0.87	*1.24 (0.90–1.71)*	*0.19*

Abbreviations: DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin.

[a]p_{trends} were computed by assigning consecutive scores (scores of 1, 2, 3) to the categories.

[b]On the log2 variable, ORs for a doubling of level of the biomarker.

[c]Based on distribution of controls.

[d]Logistic regression conditional on matching factors.

[e]Logistic regression conditional on matching factors and adjusted for height, waist circumference, alcohol, smoke (never, ever, current), physical activity and educational level.

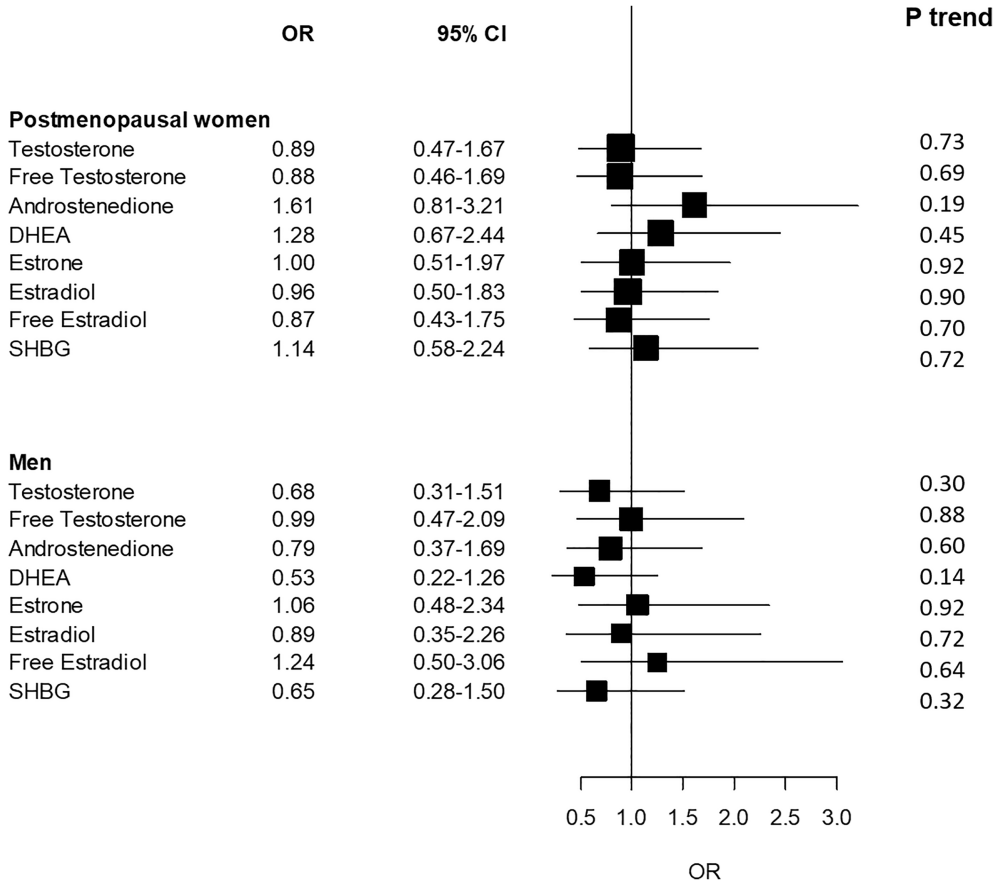

FIGURE 1 Association between sex hormone and SHBG tertiles (T3 vs T1) and differentiated thyroid cancer risk in post-menopausal women and men[$].
Notes: Number of cases/controls included: Post-menopausal women: 111/208 for testosterone, free testosterone, DHEA, androstenedione, estrone; 108/200 for estradiol and free estradiol; and 111/209 for SHBG. Men: 69/199 for testosterone, DHEA, androstenedione; 69/198 for free testosterone, estrone, estradiol; 69/197 for free estradiol; and 69/202 for SHBG.
[$] Logistic regression conditional on matching factors and adjusted for height, waist circumference, alcohol, smoke (never, ever, current), physical activity and educational level. *P*-value for trend.

T1). No significant associations were observed. All p_{trends} were above .14 (for DHEA in men) and mainly above 0.60.

4 | DISCUSSION

This is the first prospective cohort study investigating the association between circulating endogenous sex hormones, SHBG and the risk of differentiated TC in women and men. No significant associations were observed in men and postmenopausal women. In younger women, testosterone and androstenedione levels were weakly associated with an increased TC risk, while SHBG levels and progesterone/estradiol ratio were inversely associated. Overall, our results do not support the hypothesis of a strong implication of the concentrations of circulating sex steroids and SHBG in the etiology of differentiated TC in either sex, although they may

hint towards an involvement of altered sex steroid production in pre-menopausal women.

An association between sex steroid hormones and TC was suggested by a few in vivo and in vitro studies,[12,13] and by two small case–control studies. Choi et al[23] was a first study from China in which gas chromatography–mass spectrometry was used to compare urinary concentrations of 84 steroids among pre- (n = 21) and postmenopausal female (n = 19), and male (n = 16) patients with papillary TC, and gender- and age-matched controls. The urinary concentrations of androgens (androstenedione, androstenediol and 16α-hydroxy DHEA) and estrogens (estradiol, 2-hydroxy estrone and 2-hydroxy estradiol) were significantly higher in cases from premenopausal women and men compared to the corresponding controls. No differences were observed among postmenopausal women. The second case–control study,[24] included 99 Polish premenopausal patients with differentiated TC and 51 healthy women, and showed higher serum estradiol and progesterone concentrations in cases compared to controls. In addition to their limited sample size, these two previous case–control studies relied only on the comparison of means ± SD and did not provide adjusted ORs.

In the EPIC cohort, a 13% (95%CI: 1.02–1.25) increased risk in differentiated TC was observed in women with a 5 kg/m^2 increase in BMI, and especially in women below age 50, where this increase reached 24%.[25] Obesity, however, is associated with changes in SHBG and sex steroids. Indeed, in our previous study, BMI and waist circumference were negatively associated with SHBG among both pre-/perimenopausal and postmenopausal women, but positively associated with free estrogens only in postmenopausal women for whom adipose tissue is known to become a major source of estrogens.[26]

Free testosterone and free estradiol concentrations are defined as "bioavailable fractions", as only this fraction of testosterone and estradiol can enter cellular membranes and link to receptors.[22,27] SHBG is a protein produced by the liver that regulates steroids availability to the cells and is a major determinant of free testosterone concentrations.[28] Obesity and overweight, especially higher abdominal fat, causes insulin resistance and high insulin levels, which lowers hepatic production of SHBG levels, therefore increasing free testosterone concentrations.[29] In our study, however, findings about total and free testosterone were similar.

In premenopausal women, no associations with differentiated TC risk were observed with either estrogens or progesterone, when examined separately. It is, however, important to bear in mind that the levels of these hormones in premenopausal women vary substantially throughout the menstrual cycle, making a single measurement insufficient to accurately classify long-term exposure.[30] Free estradiol has been seen to be more reproducible overtime than total estradiol,[25] but no associations could be observed for this hormone either, suggesting overall that circulating estrogens do not play a major role in this disease in premenopausal women. We found a hint of a decrease in risk with the increase progesterone/estradiol ratio but this finding would require confirmation. However, it is of note that no associations with any type of circulating estrogens were found in either premenopausal or post-menopausal women.

Similarities have been proposed between the etiology of differentiated TC and breast cancer, a disease that is known to be substantially affected by reproductive and menstrual factors and by sex-hormone concentrations.[11] However, this failed to be supported by the EPIC findings on reproductive and menstrual factors and differentiated TC,[32] where no significant associations with parity, breastfeeding, and age at menarche or menopause were found. Modest but significant associations with TC were found with history of infertility, a recent pregnancy, and oral contraceptive (OC) use. An increased risk from hormone replacement therapy use lost significance after adjustment for type of menopause. From our findings, similarities between differentiated TC and breast cancer in respect to the role of sex hormones are not supported. Conversely, both diseases are influenced by medical surveillance, and metabolic pathways such as thyroid hormones or hyperinsulinemia may play a role.[11,33]

Our study has strengths and weaknesses. The prospective design, excluding possible bias of reverse causation, and the highly sensitive and specific LC/MS based method for measurements of sex steroids are clear assets, while the most important limitation is the availability of only one blood sample to assess sex steroids and SHBG concentrations. Concentrations of androgens and SHBG, for which we observed borderline associations, are fairly reproducible overtime in pre- and postmenopausal women, and men, as well as estrogens in postmenopausal women, and men, so that a single measurement could represent an individual's exposure.[31] Conversely, in premenopausal women, a single measurement of estradiol may not accurately reflect a woman's long-term sex hormone concentrations, despite our efforts to carefully match pre/peri-menopausal cases and controls by phase of menstrual cycle and compute ORs using spline regression models. Men are less subject to problems of fluctuations of hormone levels but were fewer than women.

In conclusion, the results of our studies show no clear differences in sex steroids concentrations between cases of differentiated TC and controls in either sex.

The lack of a clear relationship between the concentration of sex hormones and SHBG in women and differentiated TC risk does not exclude the possibility that other ill-understood characteristics of the female sex, for example, insufficient iodine intake, may make their thyroid gland more prone to the development of nodules and differentiated TC.[34]

AUTHOR CONTRIBUTIONS

Sabina Rinaldi: conceptualization, funding acquisition, supervision, writing-original draft; Pekka Keski-Rahkonen, Agneta Kiss, Anne-Sophie Navionis: laboratory data analyses and supervision; Carine Biessy: formal analyses; Silvia Franceschi: conceptualization, writing, review and editing; Laure Dossus Elisabete Weiderpass, Isabelle Romieu, Elom Aglago Kouassivi, Sofia Christakoudi, Marc Gunter: writing, review and editing; Ruth Travis, Anne Kirstine Eriksen, Anne Tjonneland, Marina Kvaskoff, Marianne Canonico, Thérèse Truong, Verena Katzke, Rudolf Kaaks, Alberto Catalano, Salvatore Panico, Giovanna Masala, Rosario Tumino, Marko Lukic, Karina Standahl Olsen, Raul Zamora-Ros, Carmen Santiuste, Amaia Aizpurua Atxega, Marcela

Guevara, Miguel Rodriguez-Barranco, Maria Sandstrom, Joakim Hennings, Martin Almquist: resources, writing, review and editing. All authors critically revised the manuscript for important intellectual content and have read and approved the final manuscript for publication. The work reported in the article has been performed by the authors, unless clearly specified in the text.

AFFILIATIONS

[1]International Agency for Research on Cancer (IARC/WHO), Lyon, France
[2]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]Center for Research on Population Health, National Institute of Public Health, Mexico, Mexico
[4]Danish Cancer Society Research Center, Copenhagen, Denmark
[5]Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[6]Paris-Saclay University, UVSQ, Univ. Paris-Sud, Inserm, CESP, Team "Exposome and Heredity", Villejuif, France
[7]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[8]Department of Clinical and Biological Sciences, Centre for Biostatistics, Epidemiology and Public Health, University of Turin, Turin, Italy
[9]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy
[10]Clinical Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[11]Hyblean Association for Epidemiological Research, AIRE ONLUS, Ragusa, Italy
[12]Department of Community Medicine, The Arctic University of Norway, Tromsø, Norway
[13]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
[14]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain
[15]Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[16]Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain
[17]Biodonostia Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain
[18]Instituto de Salud Pública y Laboral de Navarra, Pamplona, Spain
[19]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain
[20]Escuela Andaluza de Salud Pública (EASP), Granada, Spain
[21]Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain
[22]Department of Radiation Sciences, Oncology Umeå University, Umeå, Sweden
[23]Department of Surgical and Perioperative Sciences, Umeå University, Östersund, Sweden
[24]Department of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden
[25]Department of Surgery Section of Endocrine and Sarcoma Lund, Skåne University Hospital, Lund University, Lund, Sweden
[26]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St Mary's Campus, London, UK
[27]Department of Inflammation Biology, School of Immunology and Microbial Sciences, King's College London, London, UK
[28]CRO Aviano National Cancer Institute IRCCS, Aviano, Italy

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

All participants gave their consent for their participation to the EPIC study, and the IARC Ethics Committee and local institutional review boards in participating centers approved the study.

DISCLAIMER

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.

ORCID

Sabina Rinaldi https://orcid.org/0000-0002-6846-1204
Marina Kvaskoff https://orcid.org/0000-0002-4557-3772
Thérèse Truong https://orcid.org/0000-0002-2943-6786
Alberto Catalano https://orcid.org/0000-0003-2597-2060
Marko Lukic https://orcid.org/0000-0002-3608-9743
Raul Zamora-Ros https://orcid.org/0000-0002-6236-6804
Sofia Christakoudi https://orcid.org/0000-0001-9219-4436

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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