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Insulin-like growth factor-I and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition

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Conflict of interest
The authors declare no conflict of interest.

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Abstract

Background—Little is known about the causes of thyroid cancer, but insulin-like growth factor-I (IGF-I) might play an important role in its development due to its mitogenic and anti-apoptotic properties.

Methods—This study prospectively investigated the association between serum IGF-I concentrations and risk of differentiated thyroid carcinoma in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition. 345 incident cases of differentiated thyroid carcinoma were individually matched to 735 controls by study centre, sex, and age, date, time, and fasting status at blood collection, follow-up duration, and for women menopausal status, use of exogenous hormones, and phase of menstrual cycle at blood collection. Serum IGF-I concentrations were measured by immunoassay, and risk of differentiated thyroid cancer in relation to IGF-I concentration was estimated using conditional logistic regression.

Results—There was a positive association between IGF-I concentrations and risk of differentiated thyroid carcinoma: the odds ratio for a doubling in IGF-I concentration was 1.48

(95% confidence interval: 1.06 – 2.08; p_{trend} = 0.02). The positive association with IGF-I was stable over time between blood collection and cancer diagnosis.

Conclusion—These findings suggest that IGF-I concentrations may be positively associated with risk of differentiated thyroid carcinoma.

Impact—This study provides the first prospective evidence of a potential association between circulating IGF-I concentrations and risk of differentiated thyroid carcinoma and may prompt the further investigations needed to confirm the association.

Keywords

Insulin-like growth factor-I; differentiated thyroid carcinoma; nested case-control study

INTRODUCTION

Worldwide, the age-standardized incidence rate of thyroid cancer is 4.0 per 100,000 persons per year, with relatively high rates seen in Europe and North America (1). Thyroid cancer is three times more common in women than in men (1-4), and is now the third most common cancer in women under the age of 45 in highly developed countries (1). Papillary and follicular carcinomas, together called differentiated thyroid carcinoma, are the most common types of thyroid cancer, accounting for approximately 75% and 10% of all thyroid cancer, respectively (3, 5). There has been an increase in thyroid cancer incidence since the 1970s (3), with up to a twofold increase in some European countries (2, 3) and up to a threefold increase in the United States (3, 4), thought to be largely but not solely due to increased medical surveillance (4). Little is known about the causes of thyroid cancer with the only established risk factor being exposure to ionizing radiation, especially during childhood (6).

Insulin-like growth factor-I (IGF-I) is an endogenous hormone with mitogenic and anti-apoptotic properties (7), and high circulating concentrations have been shown to be associated with an increased risk of developing cancer at several sites, such as breast, prostate, and perhaps colorectal cancer (8-11). In contrast, there are limited epidemiological data on the relationship between IGF-I concentrations and thyroid cancer. A case-control study did not find an association between the two (12). It has been suggested that high concentrations of IGF-I may be associated with a higher risk of goitre (13), which has been linked to thyroid cancer (14-16). Furthermore, IGF-I is a determinant of height which is associated with several cancers (17) including differentiated thyroid carcinoma (18). Some small studies of patients with acromegaly, a disorder characterised by high concentrations of IGF-I, have found higher rates of differentiated thyroid cancer in this patient group than in the general population (19-21). However, it is not known whether high pre-diagnostic circulating concentrations of IGF-I are directly associated with thyroid cancer risk.

We aimed to prospectively investigate the association between serum IGF-I concentrations and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC).

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MATERIALS AND METHODS

Study population and blood collection

A detailed description of the recruitment, blood collection, and follow-up procedure in EPIC has been published previously (22). In brief, from 1992 to 2000, approximately 520,000 participants, mostly aged 35 to 70 years, were recruited in 23 centres located in ten European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom). Participants provided detailed information on dietary habits, lifestyle, anthropometry, and previous disease.

At recruitment, 385,747 of the participants (74%) gave a blood sample. In most centres, the blood collection and processing were undertaken according to a standardized protocol; whole blood was transported to a local laboratory, processed within 24 hours, and stored in liquid nitrogen (−196°C) at the International Agency for Research on Cancer (IARC), Lyon, France. Exceptions to the standardized protocol occurred; in Oxford, United Kingdom, samples were sent at ambient temperature to a laboratory in Norfolk, United Kingdom, with a mean transit time of 1.5 days; in Denmark and Sweden, all blood samples were stored locally in nitrogen vapour (−150°C) and in electric freezers (−70°C), respectively; and in Norway, serum was not collected.

Follow-up for cancer incidence and vital status

Follow up for cancer incidence and vital status was conducted via record linkage with regional and national cancer and mortality registers, except in France, Germany, and Greece. In these countries, information on cancer incidence was collected via active follow-up through participants and their next-of-kin and verified through health insurance records, and cancer and pathology registries or reports. Information on vital status was collected via active follow-up in Germany and Greece.

Selection of cases and controls

Cases were selected from cohort participants who had donated a blood sample, were free of cancer at baseline (except non-melanoma skin cancer), were diagnosed with incident thyroid cancer (WHO International Classification of Disease 10th revision code C73) before the end of follow-up, and had not been diagnosed with other tumours (except non-melanoma skin cancer), prior to the thyroid cancer diagnosis. The end of follow-up was defined as the last date of complete follow-up for both vital status and cancer incidence, which ranged from December 2006 to December 2009. This analysis focused on differentiated thyroid carcinoma, i.e. papillary (morphological codes: 8050, 8260, 8340-8344, 8350, 8450-8460) and follicular carcinomas (8290, 8330-8335) (23), as this is the most common type of thyroid cancer. Participants diagnosed with rare histological types (28 medullary, 6 anaplastic, 3 other morphologies, and 1 lymphoma) were excluded, and the present study includes 345 cases. Information on tumour-node-metastasis (TNM) stage was used to group cancers into localized (T1, N0, and M0) and more advanced (≥T2, ≥N1, or M1) cancers.

Participants were eligible as controls if they had provided a blood sample at baseline and were alive and free of cancer (other than non-melanoma skin cancer) at time of the diagnosis

of the index case. Randomly chosen controls (three controls for men and two controls for women) were matched to each case according to an incidence density sampling scheme (24). The matching criteria from a parallel study of thyroid hormones and differentiated thyroid carcinoma in our cohort (25) were used; these were: study centre, sex, duration of follow-up (duration for the control must be greater than for the index case), and age (± 1 year), date (± 3 months), time of day (± 1 hour), and fasting status (< 3; 3-6; > 6 hours) at blood collection. Women were also matched by menopausal status (premenopausal; perimenopausal or unknown; postmenopausal (26, 27)), use of exogenous hormones at blood collection (yes; no), and phase of menstrual cycle at blood collection (follicular; peri-ovulatory; luteal (26)) in premenopausal women.

This study was approved by the IARC Ethics Committee and local ethics committees in the participating countries. All participants gave written informed consent.

Laboratory measurements

Laboratory analyses were performed on serum samples, except for those from Norway and Umeå, Sweden, which provided citrated plasma and EDTA plasma samples, respectively.

Concentrations of IGF-I were measured in the Cancer Epidemiology Unit laboratory in Oxford, United Kingdom, using the automated IDS-iSYS immunoassay system from Immunodiagnostic Systems (IDS) Ltd (Boldon, United Kingdom). The intra-batch coefficient of variation was 3.7% and the overall coefficient of variation was 4.7% at a mean concentration of 13.4 nmol/l. Two samples included insufficient sample, resulting in measurements available for 345 cases and 735 controls.

Measurements of circulating concentrations of thyroid-stimulating hormone (TSH), thyroglobulin (Tg), anti-Tg antibodies (TgAb), and thyroid hormones, i.e. triiodo-thyronine (T3) and thyroxine (T4), were conducted at IARC for a previous analysis in this study population (25). Total and free T3 and T4 were measured using direct radioimmunoassay, TSH using direct immunoradiometric assays (Beckmann Coulter, Marseille, France), and Tg and tgAb using immunoradiometric assays (DiaSorin, Saluggia, Italy). Individuals with TgAb > 100 UI/ml were categorised as TgAb-positive.

Statistical analysis

Participant characteristics were compared between cases and controls within matched sets, for men and women separately, using the weighted paired-sample t-test and the likelihood ratio χ^2 test where appropriate. No p-value was calculated for matching variables. For cases only, years between blood collection and diagnosis, age at diagnosis, TNM stage (localized; more advanced), and histological type (papillary; follicular) were additionally investigated. History of thyroid disease was not systematically available in EPIC.

Concentrations of IGF-I were transformed logarithmically to approximate the normal distribution in all analyses. Geometric means of IGF-I concentrations by participant characteristics adjusted for age at blood collection (as a continuous variable), BMI (in fifths based on the distribution in controls), and sex were investigated using analysis of variance, in controls only. Analyses further adjusted for country were also conducted. Tests for linear

trend across categories were performed by scoring categories with consecutive whole numbers.

Correlations between concentrations of IGF-I and TSH, Tg, and thyroid hormones were examined in controls by use of partial correlation adjusted for age at blood collection (as a continuous variable), BMI (in fifths based on the distribution in controls), and sex. Concentrations of all analytes, except total T3, were logarithmically transformed to approximate the normal distribution. As presence of TgAb can affect the measurement of Tg concentrations, participants positive (n = 142) or unknown (n = 11) for TgAb were excluded from all analysis of Tg.

Odds ratios (OR) and 95% confidence intervals (95% CI) for differentiated thyroid carcinoma by thirds of IGF-I concentrations (based on the distributions in controls) were estimated by use of conditional logistic regression, conditioned on the matching variables and adjusted for age at blood collection (as a continuous variable) to eliminate any residual confounding by age after the matching. Using sex-specific tertile cut-points did not materially change the results; therefore the combined tertile cut-points were used for all analyses.

The linear trend of IGF-I concentration with risk of differentiated thyroid carcinoma was computed using the logarithm of IGF-I concentration as a continuous variable in the conditional logistic model. As the logarithm to base 2 was used in this analysis, the ORs and 95% CIs correspond to the odds of differentiated thyroid carcinoma associated with a doubling of IGF-I concentration. Due to the incidence density sampling of controls, all ORs estimate the incidence rate ratio for the IGF-I concentrations in relation to differentiated thyroid carcinoma in the study cohort (28).

To investigate the role of potential confounders, further multivariate conditional logistic regression models were fitted. Firstly, a multivariable-adjusted model, which included variables strongly related to case status or IGF-I concentrations in this data set, i.e. age at blood collection, height, and BMI. Secondly, a further adjusted model additionally including participant characteristics previously shown to be related to IGF-I concentrations and/or risk of thyroid cancer, i.e. waist to hip ratio, alcohol, smoking, physical activity (assessed by use of Cambridge Physical Activity Index (29)), education, and in women only, age at first period, number of full term pregnancies and age at first pregnancy, and for postmenopausal women only, age at menopause. Finally, concentrations of TSH, Tg, TgAb, and thyroid hormones (in thirds based on the distribution in controls; unknown; except for TgAb: positive; negative; unknown) were added separately to the age-adjusted model.

The ORs in thirds and for a doubling of IGF-I concentrations in sub-groups, and the heterogeneity of the ORs between sub-groups, i.e. sex, age at blood collection, education, smoking, BMI, TSH, and blood processing protocol were examined. The test for heterogeneity was done by use of the likelihood ratio χ^2 test based on models with and without an interaction term between the logarithm of IGF-I concentration and the variable of interest. The age-adjusted model was used for sub-group analyses, as multivariate adjustment made little difference to the overall risk estimates.

Furthermore, the association between IGF-I and differentiated thyroid carcinoma was investigated by tumour characteristics, i.e. histological type, TNM stage, and years between blood collection and diagnosis. Controls were assigned the value of their matched case and the analysis was conducted as described for the sub-groups.

All analyses were performed in Stata Statistical Software versions 12.1 and 13.1 (StataCorp LP, Texas, United States). Two-sided p-values < 0.05 were considered statistically significant in all analyses.

RESULTS

This analysis included 345 cases, of whom 289 (84%) were women and 56 (16%) were men. Among the cases, the mean duration from blood collection to diagnosis was 6.4 years, and they were on average 57.8 years old at diagnosis. Of the 345 cases, 101 (29%) were diagnosed with localized disease and 79 (23%) with more advanced disease; stage was unknown for 165 cases (48%). 253 cases (73%) were diagnosed with papillary carcinoma, 56 cases (16%) with follicular carcinoma, and 36 cases (11%) with not otherwise specified differentiated thyroid carcinoma.

Compared to controls, female cases were on average taller, heavier, and had a higher waist to hip ratio (Table 1). No statistically significant differences were found between cases and controls in men, although cases were, on average, taller than controls.

In controls, the geometric mean IGF-I concentration was higher among individuals who were younger at blood collection and who had a lower weight (Table 2). IGF-I concentrations differed according to BMI, with the highest geometric mean IGF-I concentration in the second fifth of BMI (22.3 – 24.4 kg/m^2) and the lowest concentration in the highest fifth (> 28.6 kg/m^2). IGF-I concentration also differed by country, being lowest in Greece (15.4 nmol/l) and highest in the Netherlands (19.4 nmol/l; $p_{difference}$ = 0.004 across all countries); further adjustment for country did not influence the other associations, except for attenuation of the association with weight (results not shown).

The partial correlations between concentrations of IGF-I and TSH, Tg, and thyroid hormones in controls, adjusted for age at blood collection, BMI, and sex, were all low (correlation coefficients ranged from −0.05 to 0.03).

Cases had a higher geometric mean IGF-I concentration than controls (17.8 nmol/l; 95% CI: 17.3 – 18.4 versus 17.1; 95% CI: 16.8 – 17.5; $p_{difference}$ = 0.03), and IGF-I concentration was positively associated with risk of differentiated thyroid carcinoma; the OR for a doubling in IGF-I concentration was 1.48 (95% CI: 1.06 – 2.08; p_{trend} = 0.02) after adjustment for age at blood collection (Table 3). Compared to those in the lowest third of IGF-I concentration, those in the highest third had a 37% increased risk (OR = 1.37; 95% CI: 0.99 – 1.91) after adjustment for age at blood collection, whereas risk was not elevated in the middle third (OR = 0.99; 95% CI: 0.71 – 1.39). Additional adjustment for height and BMI did not materially change the results, whereas further adjustment for lifestyle and reproductive factors attenuated the results slightly, resulting in a borderline significant result (Table 3). Adding the concentrations of TSH, Tg, TgAb, and the thyroid hormones

separately to the age-adjusted model did not change the results markedly; the ORs for a doubling of IGF-I concentration varied between 1.45 (95% CI: 1.02 – 2.04; p_{trend} = 0.03) when adjusting for TSH and 1.61 (95% CI: 1.14 – 2.27; p_{trend} = 0.01) when adjusting for free T4, and all models stayed statistically significant.

There was no significant heterogeneity in ORs between sub-groups, including blood processing protocol (results not shown), or by tumour characteristics (Table 3). The ORs for a doubling in IGF-I concentrations were 1.69 (95% CI: 1.13 – 2.55) for papillary carcinoma and 1.13 (95% CI: 0.53 – 2.37) for follicular carcinoma.

DISCUSSION

This prospective multi-centre study suggests that IGF-I concentrations are positively related to risk of differentiated thyroid carcinoma. The prospective nature of the study design and the finding of no heterogeneity by time from blood collection to diagnosis suggest that the apparent association of IGF-I and differentiated thyroid carcinoma is not explained by any effect of pre-clinical tumours on IGF-I concentrations.

Little is known about the association between IGF-I concentrations and risk of thyroid cancer. Some relevant evidence is provided by studies of anthropometry and thyroid cancer. For example, IGF-I concentration early in life is a determinant of height, and adult height has been found to be positively associated with risk of differentiated thyroid carcinoma (18), although IGF-I in middle age appears to be only weakly associated with height (30). It is possible that IGF-I concentrations measured earlier in life might be more strongly related to risk of thyroid cancer than concentrations measured in middle age. Previous studies that have investigated IGF-I concentrations in relation to thyroid cancer have not found an association (12, 19, 20, 31). However, three of these studies were performed in patients with acromegaly, with a small numbers of cases (n = 3 to 7), and were retrospective in design. The fourth study, a case-control study did not find an association of IGF-I with thyroid cancer over all nor with its subtypes (12).

The detailed information on participant characteristics, TSH, Tg, TgAb, and thyroid hormones available in the current study allowed a thorough investigation of the influence of potential confounding. Including anthropometry and lifestyle in the models did not materially change the results, although slight attenuation was seen after adjustment for reproductive factors. However, information about benign thyroid disease, which is positively associated with thyroid cancer risk (14-16) and IGF-I concentrations (13) was not available for the majority of participants and thus we are not able to exclude the possibility of confounding by pre-existing related conditions. Family history of thyroid cancer could also be a potential confounding factor in this study. However, the familial form of thyroid carcinoma only accounts for a small proportion of papillary and follicular thyroid carcinomas (32). Furthermore, no information was available on iodine deficiency, which may be positively associated with follicular carcinoma (33, 34). However severe iodine deficiency is rare in Europe (35). We also had no information on radiation exposure.

Our findings that serum IGF-I concentration was not correlated with concentration of TSH or thyroid hormones are consistent with other reports finding no or weak associations (36, 37), and suggest that these hormones are not likely to confound the association between IGF-I concentration and differentiated thyroid carcinoma. Furthermore, additional adjustment for TSH, Tg, TgAb, and thyroid hormones did not materially change the risk estimates, despite TSH, Tg, and TgAb being associated with differentiated thyroid carcinoma in this study population (25). The opposing direction of the relationship between differentiated thyroid carcinoma and IGF-I (a positive association) and TSH (an inverse association) is intriguing. While TSH is the strongest growth factor for thyroid follicular cells, it has been suggested that low TSH concentration may lead to predisposition to malignant transformation via reduced differentiation of thyroid follicular cells (38). There is some evidence from cell studies of a joint effect of IGF-I and TSH, as IGF-I might stimulate the transcription of the TSH receptor gene in thyroid cells (39), but there was no evidence of heterogeneity between the association between IGF-I and differentiated thyroid carcinoma at low and high concentrations of TSH in the present study.

Our findings were based on a single IGF-I measurement. Moderate to high reproducibility of IGF-I over four months to 15 years has been reported (intra-class or Spearman correlation coefficients ranged between 0.4 and 0.9) (40-45). Thus, some attenuation of the association between IGF-I concentration and differentiated thyroid carcinoma is likely due to our results being based on a single IGF-I measurement, and the true association might be stronger than reported in this paper.

A limitation of the current study is the small numbers in each group in the sub-group analyses, affecting the strength of our conclusions. Thus, further larger studies should be conducted to confirm the results of the present study. Future studies might also investigate other IGFs and IGF-binding proteins in relation to risk of differentiated thyroid carcinoma.

In conclusion, the findings of the present study suggest that IGF-I concentrations may be positively associated with risk of differentiated thyroid carcinoma.

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Table 1

Characteristics of the participants by case status and sex.

	Cases		Controls		p[a]
Women					
n	289		571		
Age at blood collection (years): mean, sd	51.3	8.3	51.3	8.3	-[b]
Anthropometry: mean, sd					
Height (cm)	161.6	6.1	160.3	6.5	0.002
Weight (kg)	67.8	12.0	65.6	11.2	0.007
BMI (kg/m^2)	26.0	4.5	25.6	4.6	0.20
Waist to hip ratio[c]	0.80	0.07	0.79	0.07	0.04
Alcohol (g/d): n, %					
0	64	22.2	102	17.9	
>0–9	161	55.7	323	56.6	
10–19	39	13.5	93	16.3	
≥ 20	25	8.7	53	9.3	0.29
Smoking: n, %[c]					
Never	161	56.3	340	60.5	
Former	65	22.7	119	21.1	
Current	60	21.0	103	18.3	0.46
Physical activity: n, %[c]					
Inactive	93	33.2	168	30.5	
Moderately inactive	96	34.3	209	37.9	
Moderately active or active	91	32.5	174	31.6	0.59
Education: n, %[c]					
Less than secondary school	118	41.7	228	40.4	
Secondary school	109	38.5	221	37.4	
University degree	56	19.8	125	22.2	0.70
Menopausal status: n, %					
Premenopausal	106	44.6	212	37.1	
Perimenopausal or unknown	54	18.7	101	17.7	
Postmenopausal	129	44.6	258	45.2	-[b]
Hours since last meal at blood collection: n, %[c]					
< 3	123	44.6	242	44.3	
3–6	50	18.1	95	17.4	
> 6	103	37.3	209	38.3	-[b]
Men					
n	56		164		
Age at blood collection (years): mean, sd	51.5	9.3	51.7	9.4	-[b]

	Cases		Controls		p[a]
Anthropometry: mean, sd					
Height (cm)	176.1	6.5	174.5	5.8	0.14
Weight (kg)	81.1	11.7	81.0	10.9	0.99
BMI (kg/m^2)	26.1	2.9	26.6	3.2	0.21
Waist to hip ratio[c]	0.94	0.07	0.94	0.06	0.98
Alcohol (g/d): n, %					
0	5	8.9	7	4.3	
> 0–9	20	35.7	58	35.4	
10–19	9	16.1	40	24.4	
≥ 20	22	39.3	59	36.0	0.40
Smoking: n, %[c]					
Never	18	33.3	52	31.7	
Former	21	38.9	65	39.7	
Current	15	27.8	47	28.7	0.99
Physical activity: n, %[c]					
Inactive	11	20.0	27	16.5	
Moderately inactive	21	38.2	70	42.7	
Moderately active or active	23	42.8	67	40.9	0.75
Education: n, %[c]					
Less than secondary school	17	32.1	48	29.5	
Secondary school	22	41.5	64	39.3	
University degree	14	26.4	51	31.2	0.83
Hours since last meal at blood collection: n, %[c]					
< 3	20	37.0	68	43.0	
3–6	12	22.2	22	13.9	
> 6	22	40.7	68	43.0	-[b]

[a] The weighted paired-sample t-test and the likelihood ratio χ^2 test from conditional logistic regression were used for continuous and categorical variables, respectively.

[b] No p-value was calculated for matching factors.

[c] Unknown for some participants; mean, sd or n, %, and tests exclude unknown values.

Table 2

Adjusted geometric mean IGF-I concentrations (nmol/l) and 95% CI in 735 controls.

	n	Geometric mean and 95% CI[a]			$p_{difference}$[b]	p_{trend}[c]
All controls	735	17.1	16.8	17.5	–	–
Sex						
Male	164	17.5	16.7	18.3		
Female	571	17.0	16.6	17.4	0.33	–
Age at blood collection (years)						
< 48	253	19.3	18.6	20.0		
48–55	253	16.8	16.2	17.4		
≥ 56	229	15.3	14.7	15.9	< 0.0001	< 0.0001
Height (cm)						
<160	253	17.2	16.5	17.9		
160–164	182	17.5	16.7	18.3		
165–169	134	17.6	16.8	18.4		
≥170	166	16.3	15.4	17.3	0.27	0.62
Weight (kg)						
< 60	187	17.8	17.1	18.6		
60–69	247	17.2	16.6	17.9		
70–79	162	17.1	16.4	17.9		
≥ 80	139	16.1	15.3	16.9	0.04	0.01
BMI (kg/m^2)						
<22.3	147	17.5	16.7	18.3		
22.3–24.4	146	18.1	17.3	19.0		
24.4–26.3	147	17.4	16.7	18.3		
26.3–28.6	148	16.8	16.0	17.6		
> 28.6	147	15.9	15.2	16.6	0.001	0.0003
Waist to hip ratio[d]						
< 0.76	163	17.6	16.7	18.5		
0.76–0.80	160	17.5	16.7	18.4		
0.81–0.88	195	17.3	16.6	18.0		
≥ 0.89	177	16.5	15.5	17.6	0.58	0.27
Alcohol (g/d)						
0	109	16.5	15.6	17.4		
> 0–9	381	17.2	16.8	17.7		
10–19	133	17.0	16.2	17.9		
≥ 20	112	17.5	16.6	18.5	0.42	0.26
Smoking[d]						
Never	392	17.2	16.7	17.7		
Former	184	17.4	16.6	18.1		
Current	150	16.7	16.0	17.5	0.51	0.50

	n	Geometric mean and 95% CI[a]			$p_{difference}$[b]	p_{trend}[c]
Physical activity[d]						
Inactive	195	16.8	16.1	17.5		
Moderately inactive	279	17.1	16.6	17.7		
Moderately active or active	241	17.5	16.9	18.1	0.37	0.16
Education[d]						
Less than secondary	276	16.8	16.2	17.4		
Secondary school	275	17.6	17.0	18.2		
University degree	176	17.1	16.4	17.8	0.16	0.42
Menopausal status[e]						
Premenopausal	212	17.2	16.3	18.2		
Perimenopausal or unknown	101	16.5	15.6	17.5		
Postmenopausal	258	17.2	16.4	18.0	0.44	–
Hormone replacement therapy at blood collection[d,e]						
No	462	17.1	16.7	17.6		
Yes	95	17.2	16.2	18.2	0.94	–
Hours since last meal at blood collection[d]						
< 3	310	17.0	16.5	17.6		
3–6	117	16.9	16.1	17.8		
> 6	277	17.5	17.0	18.1	0.35	0.21

[a] Adjusted for age at blood collection (as a continuous variable), BMI (in fifths based on the distribution in controls), and sex, where the adjustment variable was not the variable of interest. Analysis of weight was not adjusted for BMI.

[b] P values refer to tests of difference between the logarithm of IGF-I concentration in the separate categories (excluding unknowns) calculated by analysis of variance.

[c] P values refer to tests of linear trend calculated by scoring categories with consecutive whole numbers (excluding unknowns).

[d] Unknown for some participants.

[e] In women only.

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Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 December 01.

Table 3

Odds ratios and 95% CI for differentiated thyroid carcinoma associated with thirds and a doubling of IGF-I concentration, overall, by sub-groups, and by tumour characteristics.

		Bottom third			Middle third			Top third			Doubling[a]				
	IGF-I range (median)	< 15.3 (13.0) nmol/l[b]			15.3 - 19.6 (17.4) nmol/l[b]			> 19.6 (22.8) nmol/l[b]							
		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		P_{trend}	$P_{heterogeneity}$[c]
	$n_{case}/n_{control}$	105/245			101/245			139/245							
Risk overall[d]															
Age-adjusted model	**345/735**	**1**	**Ref**		**0.99**	**0.71**	**1.39**	**1.37**	**0.99**	**1.91**	**1.48**	**1.06**	**2.08**	**0.02**	–
Multivariable-adjusted model[e]	**345/735**	**1**	**Ref**		**1.00**	**0.71**	**1.41**	**1.37**	**0.98**	**1.92**	**1.46**	**1.04**	**2.07**	**0.03**	–
Further adjusted model[f]	**345/735**	**1**	**Ref**		**1.02**	**0.72**	**1.46**	**1.33**	**0.93**	**1.88**	**1.41**	**0. 99**	**2.01**	**0.06**	–
Risk in sub-groups[d]															
Sex															
Male	56/164	1	Ref		1.01	0.45	2.28	1.63	0.73	3.65	1.39	0.61	3.16	0.43	
Female	289/571	1	Ref		0.99	0.68	1.44	1.33	0.92	1.91	1.50	1.04	2.18	0.03	0.87
Age at blood collection (years)															
< 50	146/310	1	Ref		1.55	0.84	2.84	1.59	0.91	2.78	1.54	0.90	2.66	0.12	
≥ 50	199/425	1	Ref		0.79	0.52	1.20	1.39	0.91	2.13	1.45	0.94	2.22	0.09	0.86
Education[g]															
Less than secondary school	135/273	1	Ref		1.10	0.66	1.86	1.47	0.87	2.48	1.80	1.08	3.00	0.02	
Secondary school or more	201/436	1	Ref		0.84	0.53	1.31	1.20	0.79	1.83	1.27	0.83	1.93	0.27	0.27
Smoking															
Never	179/390	1	Ref		1.02	0.65	1.60	1.37	0.87	2.17	1.62	1.03	2.56	0.04	
Ever	161/326	1	Ref		0.96	0.58	1.58	1.39	0.87	2.24	1.39	0.88	2.20	0.16	0.62
BMI (kg/m^2)															
< 25	158/347	1	Ref		0.92	0.55	1.53	1.32	0.81	2.16	1.45	0.88	2.38	0.14	
≥ 25	187/388	1	Ref		1.05	0.67	1.64	1.44	0.92	2.26	1.55	1.00	2.42	0.05	0.84
Thyroid stimulation hormone (mIU/l)[g]															

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		Bottom third		Middle third			Top third			Doubling[a]				
	IGF-I range (median)	< 15.3 (13.0) nmol/l[b]		15.3 - 19.6 (17.4) nmol/l[b]			> 19.6 (22.8) nmol/l[b]							
		OR	95% CI	OR	95% CI		OR	95% CI		OR	95% CI		P_{trend}	$p_{heterogeneity}$[c]
< 1.27	204/365	1	Ref	1.03	0.66	1.61	1.37	0.89	2.11	1.46	0.96	2.22	0.08	
≥ 1.27	140/366	1	Ref	1.00	0.59	1.67	1.35	0.83	2.22	1.52	0.91	2.52	0.11	0.90
Risk by tumour characteristics[d]														
Histological type[g]														
Papillary	253/538	1	Ref	1.30	0.86	1.95	1.62	1.09	2.40	1.69	1.13	2.55	0.01	
Follicular	56/122	1	Ref	0.60	0.27	1.38	0.92	0.41	2.08	1.13	0.53	2.37	0.76	0.35
TNM stage[g]														
Localized	101/211	1	Ref	0.92	0.47	1.78	1.48	0.82	2.70	1.44	0.81	2.54	0.22	
More advanced	79/172	1	Ref	2.01	1.00	4.06	1.53	0.75	3.13	1.91	0.90	4.08	0.09	0.55
Years between blood collection and diagnosis														
< 5	137/293	1	Ref	0.79	0.46	1.35	1.33	0.80	2.21	1.48	0.84	2.61	0.18	
≥ 5	208/442	1	Ref	1.15	0.74	1.80	1.42	0.92	2.20	1.48	0.97	2.26	0.07	0.99

[a] OR, 95% CI, and p_{trend} were based on the logarithm (base2) of IGF-I concentrations (as a continuous variable) and correspond to the risk associated with a doubling in IGF-I concentration.

[b] Tertile cut-points were based on the distribution controls only.

[c] P values refer to likelihood ratio χ^2 test between models of the linear trend in logarithm (base 2) of IGF-I concentrations with and without an interaction term with the variable of interest.

[d] All analyses were logistic regression models conditioned on the matching variables and adjusted for age at blood collection (as a continuous variable).

[e] The multivariable-adjusted model was adjusted for age at blood collection (as a continuous variable), height (as a continuous variable), and BMI (in fifths based on the distribution in controls).

[f] The further adjusted model was in addition to age at blood collection, height, and BMI adjusted for waist to hip ratio (below and above the median based on the distribution in controls; unknown), alcohol (0; > 0 – 9; 10 – 19; ≥ 20 g/d), smoking (never; former; current; unknown), physical activity (inactive; moderately inactive; moderately active or active; unknown), education (less than secondary school; secondary school; university degree; unknown), and in women only, age at first period (< 12; 12 – 14; < 14 years; unknown), number of full term pregnancies and age at first pregnancy (nulliparous; 1 – 2 children and < 25 years; 1 – 2 children and ≥ 25 years; ≥ 3 children and < 25 years; ≥ 3 children and ≥ 25 years; unknown), and for postmenopausal women only, age at menopause (<50; ≥ 50 years; unknown).

[g] Unknown for some participants.