Energy and macronutrient intake and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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Abstract

Incidence rates of differentiated thyroid carcinoma (TC) have increased in many countries. Adiposity and dietary risk factors may play a role, but little is known on the influence of energy intake and macronutrient composition. The aim of this study is to investigate associations between TC and the intake of energy, macronutrients, glycemic index (GI) and glycemic load in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The study included 477,274 middle-age participants (70.2% women) from 10 European countries. Dietary data were collected using country-specific validated dietary questionnaires. Total carbohydrates, proteins, fats, saturated, monounsaturated and polyunsaturated fats (PUFA), starch, sugar, fiber and glycemic load were computed as g/1000kcal. Multivariable Cox regression was used to calculate multivariable adjusted hazard ratios (HR) and 95% confidence interval (CI) by intake quartile (Q). After a mean follow-up time of 11 years, differentiated TC was diagnosed in 556 participants (90% women). Overall, we only found significant associations with total energy (HR_{Q4vsQ1} 1.29; 95% CI 1.00-1.68) and PUFA intakes (HRQ4vsQ1 0.74, 95% CI 0.57-0.95). However, the associations with starch and sugar intake and GI were significantly heterogeneous across BMI groups, i.e., positive associations with starch and GI were found in participants with a body mass index (BMI) 25 and with sugar intake in those with BMI <25. Moreover, inverse associations with starch and GI were observed in subjects with BMI<25. In conclusion, our results suggest that high total energy and low PUFA intakes may increase the risk of differentiated TC. Positive

associations with starch intake and GI in participants with BMI ≥ 25 suggest that those persons may have a greater insulin response to high starch intake and GI than lean people.

Keywords

macronutrients; total energy; glycemic index; differentiated thyroid carcinomas; EPIC

Introduction

Thyroid carcinoma (TC) is the most common endocrine cancer and its incidence has steadily increased in the last three decades in many countries.[1,2] Upward trends of differentiated TC, by far the most common type of TC, are clearly correlated with the introduction of ultrasonography and other imaging techniques since the late 1970s and the use of fine-needle biopsies for assessment of thyroid nodules. However, a role of lifestyle factors, including dietary habits, and environmental exposures is possible and ill-understood.[1] The only well-established TC risk factors are ionizing radiation,[3] benign thyroid disease,[4] and high body mass (including weight and height).[5,6] Although thyroid nodules and well-differentiated TC are more often detected in women than men, the associations with individual reproductive and menstrual factors and female hormone use are, if anything, weak.[7]

Dietary factors including some food groups (fish, shellfish, meat, starchy foods, fruits, and vegetables),[8,9] macro-nutrients,[10] vitamins, micro-elements (iodine, nitrate, nitrites),[8,11–13] glycemic index (GI) and load (GL),[14] and local traditional dietary patterns (Polynesian dietary pattern)[15,16] have been studied in respect to TC risk. However, findings were mainly based on case-control studies and are inconclusive.[8,9] Chronic iodine deficiency is the only dietary recognized risk factor for goiter and follicular TC.[8]

The aim of the current study is to evaluate prospectively the relationships between total energy intake, macronutrient composition (including sugar, starch, fiber and fats), GI and GL and the risk of developing differentiated TC in a large European cohort: the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Material and Methods

Study Population

EPIC is a multi-center, prospective cohort that was designed to study the role of dietary and environmental factors in the risk of developing cancer. Details on the EPIC study have been published previously.[17,18] Briefly, a total of 521,330 subjects (70.6% women) aged mainly 35–70 years were recruited between 1992 and 2000, primarily from the general population, in 23 centers from 10 western European countries. All participants gave written informed consent and the project was approved by ethical review boards of the International Agency for Research on Cancer and local participating centers.

Dietary and Lifestyle Data

Data collection includes participants' habitual dietary intake during the year prior to recruitment using country-specific validated dietary questionnaires.[18,19] Total energy and macronutrient intakes were estimated by using the standardized EPIC Nutrient Database.[20] Carbohydrates are calculated as the sum of all "available carbohydrates" (sugars, oligosaccharides and starch) and do not include fibers. Both dietary GI and GL were estimated as previously described.[21] Briefly, the average dietary GI for each subject was calculated as the sum of the GIs of each food item consumed, multiplied by the average daily amount consumed and the percentage of carbohydrate content, all divided by the total daily carbohydrate intake. The GL was calculated similarly except that there was no division by total carbohydrate intake. Each unit of GL is equivalent to the blood glucose-raising effect of consuming 1 g of glucose. At baseline, information on socio-demographic characteristics, tobacco consumption, physical activity according to the Cambridge Physical Activity Index,[22] education, and medical history was self-reported using standardized lifestyle questionnaires.[18,22] In most centers, weight and height at recruitment were measured; except for Oxford-UK, France, and Norway, where self-reported anthropometric values were collected.

Follow-up and case ascertainment

Incident cancer cases and deaths were identified through population-based cancer registries and mortality registries or active follow-up, depending on the center. Censoring dates for the last complete follow-up ranged from December 2006 to December 2009, depending on the study center. Cases were defined as subjects with a first primary TC (code C73 according to the International Classification of Diseases, ICD-10) during follow-up.

Of 604 TC cases, anaplastic (n=6), medullary (n=28) and TC defined as lymphoma (n=1), or "other morphologies" (n=3) were excluded. We also excluded 28,151 participants (including 1 differentiated TC case) with prevalent cancer other than non-melanoma skin cancer, and 15,867 participants (including 9 differentiated TC cases) for whom dietary information was unavailable or considered to be implausible, i.e., participants who were in the top or the bottom 1% of the distribution of the ratio of total energy intake to energy requirement.[23] A total of 477,274 men and women and 5,262,772 person-years of observation (mean follow-up time of 11 years) were included in the present analysis. A total of 556 primary differentiated TC cases were retained for the present report including 435 papillary, 76 follicular, and 45 not otherwise specified TC, most likely to be also papillary TC.

Statistical analysis

Total energy intake was included in the models as kcal/day. Carbohydrate, lipids, protein, saturated, monounsaturated and polyunsaturated fats (PUFA), sugar, starch and fiber intakes were computed as energy density (g/1000kcal) per day. GL was calculated as units/1000kcal per day, while GI was computed as units/day (since GI values reflect the physiological response to the consumption of the food item, but not its quantity). Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for the intake of all dietary exposures of interest in relation to differentiated TC risk. Tests and graphs based on Schoenfeld residuals were used to assess proportional hazards assumptions,

which were satisfied. Age was used as primary dependent time variable, with entry time defined as the subject's age at recruitment and exit time as age at differentiated TC diagnosis, death or censoring date (lost or end of follow-up), whichever occurred first. Model 1 was stratified by sex, age at recruitment (1-year intervals), and center. Model 2 was additionally adjusted for body mass index (BMI, kg/m^2), smoking status (never, former, current smoker, and unknown), education level (primary, secondary, and unknown), physical activity (inactive, active, and unknown), total energy (kcal/d) except when total energy is the main exposure, and alcohol intake (g/d). In women Model 2 also included menopause status, type of menopause (pre-, peri-, post-menopausal, surgical menopause).7 Oral contraceptive use (yes, no, and unknown) and history of infertility problems (yes, no, and unknown) were not included in final models because they did not change effect estimates by more 10%. In a secondary analysis, model 2 was mutually adjusted, when appropriate, for protein, saturated, monounsaturated and polyunsaturated fats, sugar, starch and fiber intakes (g/d). Dietary exposures were assessed by cohort-wide quartiles or BMI-, age-, or sex-specific quartile in stratified analyses. Tests for linear trend were performed by assigning the medians of each quartile as scores. Separate analyses were performed for papillary TC and strata of BMI, waist circumference, sex and age. Possible interactions with sex, age (<50 vs. 50 years), BMI (<25 vs. 25kg/m^2), waist circumference (88 vs. >88 in women and 102 vs. >102cm in men), physical activity index and smoking status were examined by including the interaction terms in the most adjusted models. Interactions were tested to evaluate whether separate analyses, stratified according to each variable, were required. The Wald test was used to evaluate the heterogeneity of risk trends across sex, age, BMI or waist circumference strata. Three types of sensitivity analyses were performed by excluding them from the analyses: 1) 67,378 women from the French component of EPIC (202 cases of differentiated TC), since French women represented the 40.5% of TC cases in women; 2) 14,856 participants who had diabetes or unknown diabetes status at baseline (11 cases of differentiated TC), because diabetes is a potential risk factor of TC; and 3) 81 cases in whom differentiated TC was diagnosed in the first 2 years of follow-up, because some participants may have modified their diet during the early prediagnostic period of the disease. We considered 2-tailed P-values 0.05 to be statistically significant. Statistical analyses were conducted using SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics of participants with and without differentiated TC are shown in Table 1. Cases were predominantly women (89.7%) and median age at baseline was 50.0 among women and 51.7 among men. Median BMI, alcohol intake, percentages of never-smokers, secondary education, physical inactivity, and diabetes did not differ by case status. More female cases than non-cases were peri-menopausal or had undergone surgical menopause (Table 1).

Table 2 shows the relationship between differentiated TC risk and energy intake, energy density of various macronutrients, and GI and GL. Total energy intake was borderline positively associated with differentiated TC risk in Model 2 analyses [HR$_{Q4vsQ1}$ 1.29, 95% CI 1.00-1.68; P-trend = 0.06]. A significantly inverse association with PUFA intake was also found in Model 2 analyses (HR $_{Q4vsQ1}$ 0.74, 95% CI 0.57-0.95; P-trend = 0.028) (Table 2).

In models mutually adjusted, results were similar to HRs observed in model 2 but with wider 95% CI, especially for PUFA where the inverse associations became not significant (HR $_{Q4vsQ1}$ 0.73, 95% CI 0.49-1.08; P-trend = 0.15). No significant associations were observed with energy density of carbohydrates, fat, saturated and monounsaturated fats, protein, starch, sugar, fiber, and GI and GL in either model. Similar HRs were found in analyses restricted to papillary TC (Supplemental table 1).

The interactions between BMI group and the intake of starch, sugar, and GI were statistically significant (P-value for interaction = 0.032, 0.025, and 0.011, respectively), and therefore BMI-stratified Model 2 analyses were performed for carbohydrate-related nutrients, fiber, and GI and GL (Table 3). Significant positive associations were observed for starch intake (HR$_{Q4vsQ1}$ 1.52, 95% CI 1.02-2.28; P-trend = 0.020) and GI (HR$_{Q4vsQ1}$ 1.54, 95% CI 1.05-2.28; P-trend = 0.014) among participants with BMI ≥25. Conversely, in participants with BMI <25 starch intake (HR$_{Q4vsQ1}$ 0.64, 95% CI 046-0.89; P-trend = 0.003) and GI (HR$_{Q4vsQ1}$ 0.64, 95% CI 0.46-0.89; P-trend = 0.003) were inversely associated with differentiated TC risk and sugar intake was positively associated (HR$_{Q4vsQ1}$ 1.61, 95% CI 1.16-2.24; P-trend = 0.002). Similar associations were observed after stratifying by waist circumference (data not shown).

In a separate analysis by sex, a significant positive association was detected with total carbohydrate intake in men (HR$_{Q4vsQ1}$ 4.15, 95% CI 1.37-15.22; P-trend = 0.019) (Supplemental table 1). The interaction between carbohydrate intake and TC risk by sex was statistically significant (P-value for interaction = 0.022). In a separate analysis by age groups (<50y vs. ≥50y), similar results as the entire cohort were found, highlighting the significant inverse association with PUFA in older subjects (HR$_{Q4vsQ1}$ 0.63, 95% CI 0.44-0.92; P-trend = 0.024) (Supplemental table 1). No statistically significant interactions of dietary habits with smoking status or physical activity level were observed.

Results similar to those of Table 2 and 3 were observed in sensitivity analyses in which the French EPIC component, participants with diabetes, and TC cases who had been diagnosed within the first 2 years of follow-up were excluded (data not shown).

Discussion

The current large European prospective cohort study suggests that high total energy and low PUFA intakes may increase the risk of differentiated TC. Among all study participants, the intake of carbohydrates, proteins, and fat were not related to differentiated TC risk. However, positive associations with starch intake, and GI were statistically significant among persons with BMI ≥25 and statistically heterogeneous from findings in leaner persons. Conversely, a positive association with sugar intake was found among subjects with BMI<25 and was statistically heterogeneous from findings in persons with BMI ≥25. No differences in TC risk by intake of proteins, fat, or fiber were found in either overall analyses or in analyses stratified by BMI, sex, or age group. Although the large increases in the incidence of very seldom fatal differentiated TC is attributed to the increased surveillance of the thyroid gland and the advent of more sensitive diagnostic methods,24 increases in

overweight, insulin resistance, and refined carbohydrate intake over the last 20 years may have played a role.

Very little information is available on the relationship between TC risk and the intake of energy and main energy sources. Case-control studies from Brazil,10 Italy,25 and Poland26 showed that higher intake of energy, and rich-carbohydrate sources among TC cases as compared to controls. In a case-control study from French Polynesia, bread, rice and pasta were included in a "Western dietary pattern" that was also positively associated with elevated risk of differentiated TC.15 Positive associations with elevated GI and GL were reported from Italy.14 GI and GL are indicators of the physiological response to different foods in terms of plasma glucose and insulin response27 and are highly correlated with high intake of refined carbohydrates.

Our results raise the possibility that BMI may be a modifier of the association of high-energy and high-GI diet with the risk of differentiated TC. Overweight is a major determinant of insulin resistance and hyperinsulinemia,28 which were associated with a higher prevalence of differentiated TC.29 Our results may therefore point to a stronger insulin response to diet in individuals with BMI 25 than in those with BMI<25 which may affect TC risk. The findings on sugar seem to be contradictory as the adverse effect of high intake is restricted to subjects with BMI<25. Individuals with overweight may voluntarily reduce their sugar intake, as suggested by the slightly lower sugar intake in subjects with BMI 25 compared to those with BMI<25 (Table 3). Under-reporting of sugar intake among over-weight people is also possible.

Hyperglycemia, insulin resistance, and obesity increase oxidative stress and stimulate mitogenic pathways of follicular thyroid cells.30 The growth-promoting effect of insulin and insulin-like growth factor-I (IGF-I) have also been proposed as a causal link between abnormal glucose metabolism and cancer risk and doubling in IGF-I concentration is associated with a relative risk of 1.48 (95% CI: 1.06–2.08) for differentiated TC in the EPIC study.31 Moreover, a recent meta-analysis showed that subjects with diabetes have a higher risk for TC, particularly women.32 High blood glucose levels were also associated with a higher prevalence of thyroid nodules and TC in Chinese studies.33,34 However, in a European cohort study, blood glucose level was associated with a significantly decreased risk of incident TC35 and no association between fasting serum insulin and TC in both genders was observed in a screening program of TC in the Republic of Korea.36

Our findings on total energy intake need to be interpreted with caution as energy intake and energy expenditure are crudely measured.37 Obviously, diets high in energy and starch can increase the risk of having larger waist circumference and developing overweight and obesity that are associated with differentiated TC risk.5,6 In fact, energy intake at baseline was marginally larger in participants with BMI 25 than in those with BMI<25 (Table 3), possibly reflecting a gradual gain in weight.

In respect to fat intake, our study shows an inverse association between PUFA intake and differentiated TC risk in agreement with a Norwegian case-control study in which high serum levels of PUFA, particularly arachidonic and docosahexaenoic acids, were associated

with a reduced TC risk.38 Moreover, two case-control studies found significantly lower urinary or serum levels of PUFA in TC cases than in controls.39,40 In EPIC, the main food sources of PUFA intake are vegetable oils, nuts and seeds, and fish.41 Vegetable oils and especially nuts and seeds are rich in polyphenols that are well-known for having several anticarcinogenic effects and have been inversely associated with TC risk in a large cohort study.13 The influence of fish consumption on TC risk has been investigated in numerous studies,42 as salt-water fish is a major source of dietary iodine. However, results are not conclusive.8,9

Strengths of the present study include the prospective design, the completeness of follow-up and dietary questionnaire, and the inclusion of participants from cohorts across 10 European countries with widely varying dietary habits. Our analyses were adjusted for a comprehensive range of potential confounders, including alcohol drinking that shows an inverse association with TC risk.9 Obviously, measurement errors in the dietary questionnaire may have attenuated our dietary findings or left residual confounding effects from total energy and physical activity levels. Modification of diet in the years prior to a diagnosis of differentiated TC is unlikely and the exclusion of cases diagnosed in the first two years of follow-up did not alter our findings. Diabetics were not overrepresented among TC cases and, again, the exclusion of EPIC participants who were diabetic at baseline had no material influence.

In conclusion, this large prospective study suggests a direct association between differentiated TC risk and total energy intake and an inverse association with dietary PUFA intake. Positive associations with starch intake and GI, but not sugar, in subjects with BMI ≥ 25 encourages further study of the combined influence of diet, BMI, insulin resistance, and related serum markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

BMI	body mass index
CI	confidence interval
EPIC	European Prospective Investigation into Cancer and Nutrition
GI	glycemic index
GL	glycemic load
HR	hazard ratio
CI	confidence interval
IGF-I	insulin-like growth factor -I
PUFA	polyunsaturated fats
TC	thyroid carcinoma

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Novelty and Impact of the Work

This large prospective cohort supports positive and inverse associations of total energy intake and dietary polyunsaturated fat intake respectively with differentiated thyroid carcinoma risk. However, the associations with carbohydrate-related variables were heterogeneous across BMI groups, suggesting that diet and slimness may interact to protect against this carcinoma.

Table 1

Baseline characteristics of participants in the EPIC study by onset of differentiated thyroid carcinoma (TC) at follow up and sex

Characteristics	Women		Men	
	Non-cases (n=334,534)	TC cases (n=499)	Non-cases (n=142,184)	TC cases (n=57)
Country (%)				
France	20.1	40.5	—	—
Italy	9.1	13.0	9.9	29.8
Spain	7.4	9.6	10.7	5.3
United Kingdom	15.7	5.0	16.1	7.0
The Netherlands	8.0	2.0	6.8	3.5
Greece	4.5	3.8	7.6	8.8
Germany	8.2	13.0	14.9	24.6
Sweden	7.9	3.8	15.7	8.8
Denmark	8.6	3.2	18.5	12.3
Norway	10.5	6.0	—	—
Median age (27-75%) (years)	51.0 (44.9-57.5)	50.0 (45.8-55.9)	52.7 (45.7-59.6)	51.7 (44.7-58.2)
Median BMI (25-75%) (kg/m^2)	24.1 (21.9-27.2)	24.1 (22.0-27.3)	26.1 (24.0-28.6)	26.0 (24.3-27.7)
Median alcohol (25-75%) (g/d)	3.3 (0.5-10.7)	2.9 (0.4-9.8)	12.5 (3.9-29.2)	12.1 (2.2-28.7)
Never smokers (%)[1]	57.0	59.1	33.4	34.6
Secondary education (%)[1]	70.5	68.6	65.4	68.5
Physical inactivity (%)[1]	60.1	63.3	50.5	57.1
Diabetes at baseline (%)[1]	2.4	1.9	4.0	3.6
Menopause status and type (%)				
Premenopausal	34.8	33.7	—	—
Perimenopausal	18.9	24.8	—	—
Natural menopause	43.4	36.1	—	—
Surgical menopause	2.9	5.4	—	—

[1]Percentages were calculated among participants with available data

Table 2

Hazard ratios (HR) and 95% confidence intervals for differentiated thyroid cancer according to quartile of intake of total energy, macronutrients, glycemic index and load in the EPIC study.

		Thyroid carcinoma		
	Intake	No of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total energy (kcal/d)				
Quartile 1	<1,630	128	1 (ref)	1 (ref)
Quartile 2	1,630-1,995	142	1.08 (0.85-1.38)	1.11 (0.87-1.42)
Quartile 3	1,996-2,435	139	1.06 (0.82-1.36)	1.11 (0.86-1.43)
Quartile 4	>2,435	147	1.18 (0.91-1.53)	1.29 (1.00-1.68)
P-trend			0.23	0.06
Carbohydrates (g/1000kcal*d)				
Quartile 1	<98.6	143	1 (ref)	1 (ref)
Quartile 2	98.6-110.6	149	1.13 (0.90-1.43)	1.07 (0.84-1.35)
Quartile 3	110.7-122.4	140	1.14 (0.89-1.45)	1.05 (0.82-1.35)
Quartile 4	>122.4	124	1.12 (0.86-1.45)	1.01 (0.77-1.33)
P-trend			0.39	0.93
Protein (g/1000kcal*d)				
Quartile 1	<37.0	104	1 (ref)	1 (ref)
Quartile 2	37.0-41.6	143	1.19 (0.92-1.54)	1.16 (0.89-1.50)
Quartile 3	41.7-46.9	150	1.16 (0.89-1.51)	1.09 (0.84-1.43)
Quartile 4	>46.9	159	1.24 (0.94-1.63)	1.14 (0.86-1.51)
P-trend			0.18	0.51
Fat (g/1000kcal*d)				
Quartile 1	<34.4	108	1 (ref)	1 (ref)
Quartile 2	34.4-38.8	136	1.10 (0.85-1.41)	1.06 (0.82-1.37)
Quartile 3	38.9-43.3	154	1.12 (0.87-1.44)	1.05 (0.82-1.36)
Quartile 4	>43.3	158	0.98 (0.76-1.28)	0.90 (0.69-1.18)
P-trend			0.82	0.38
Saturated fats (g/1000kcal*d)				
Quartile 1	<12.5	115	1 (ref)	1 (ref)
Quartile 2	12.5-14.7	114	0.95 (0.73-1.24)	0.93 (0.71-1.21)
Quartile 3	14.8-17.1	170	1.34 (1.04-1.73)	1.29 (1.00-1.66)
Quartile 4	>17.1	157	1.07 (0.82-1.40)	1.01 (0.77-1.32)
P-trend			0.34	0.63
Monounsaturated fats (g/1000kcal*d)				
Quartile 1	<11.6	103	1 (ref)	1 (ref)
Quartile 2	11.6-13.4	131	1.07 (0.82-1.40)	1.05 (0.81-1.36)
Quartile 3	13.5-16.0	162	1.13 (0.87-1.46)	1.09 (0.84-1.41)
Quartile 4	>16.0	160	0.96 (0.71-1.30)	0.90 (0.67-1.22)

	Intake	No of cases	Thyroid carcinoma	
			Model 1 HR (95% CI)	Model 2 HR (95% CI)
P-trend			0.72	0.44
Polyunsaturated fats (g/1000kcal*d)				
Quartile 1	<4.9	159	1 (ref)	1 (ref)
Quartile 2	4.9-6.0	135	0.86 (0.68-1.09)	0.84 (0.66-1.07)
Quartile 3	6.1-7.6	132	0.81 (0.63-1.04)	0.78 (0.61-1.00)
Quartile 4	>7.6	130	0.78 (0.60-1.01)	0.74 (0.57-0.95)
P-trend			0.07	0.028
Starch (g/1000kcal*d)				
Quartile 1	<47.9	140	1 (ref)	1 (ref)
Quartile 2	47.9-57.2	140	1.12 (0.89-1.42)	1.09 (0.86-1.38)
Quartile 3	57.3-67.8	145	1.14 (0.90-1.44)	1.09 (0.86-1.39)
Quartile 4	>67.8	131	0.97 (0.75-1.25)	0.91 (0.70-1.18)
P-trend			0.82	0.47
Sugar (g/1000kcal*d)				
Quartile 1	<38.9	142	1 (ref)	1 (ref)
Quartile 2	38.9-48.4	135	0.91 (0.72-1.16)	0.89 (0.70-1.13)
Quartile 3	48.5-59.4	143	1.04 (0.82-1.31)	1.00 (0.78-1.27)
Quartile 4	>59.4	136	1.17 (0.91-1.51)	1.11 (0.85-1.43)
P-trend			0.14	0.31
Fiber (g/1000kcal*d)				
Quartile 1	<9.1	148	1 (ref)	1 (ref)
Quartile 2	9.1-10.8	135	0.83 (0.65-1.05)	0.78 (0.62-1.00)
Quartile 3	10.9-13.0	155	1.05 (0.83-1.32)	0.97 (0.76-1.24)
Quartile 4	>13.0	118	0.91 (0.70-1.18)	0.83 (0.63-1.09)
P-trend			0.83	0.41
Glycemic index (unit/d)				
Quartile 1	<53.6	166	1 (ref)	1 (ref)
Quartile 2	53.6-56.0	144	1.09 (0.87-1.37)	1.09 (0.87-1.37)
Quartile 3	56.1-58.5	117	0.93-0.73-1.18)	0.93 (0.73-1.19)
Quartile 4	>58.5	129	0.94 (0.73-1.20)	0.94 (0.73-1.20)
P-trend			0.47	0.46
Glycemic load (unit/1000kcal*d)				
Quartile 1	<54.4	152	1 (ref)	1 (ref)
Quartile 2	54.4-61.9	141	1.02 (0.81-1.29)	0.98 (0.77-1.23)
Quartile 3	62.0-69.6	123	1.06 (0.83-1.34)	0.99 (0.77-1.26)
Quartile 4	>69.6	140	1.04 (0.81-1.34)	0.95 (0.74-1.24)
P-trend			0.72	0.77

Model 1: Cox model stratified by center, age at baseline, and sex

Model 2: Additionally adjusted for body mass index, smoking status, education, physical activity, total energy (as appropriate) and alcohol intake, and, in women, for menopausal status and type.

Table 3

Hazard ratios (HR) and 95% confidence intervals for differentiated thyroid carcinoma stratified by body mass index (BMI) according to intake of total energy and carbohydrate-related dietary variables in the EPIC study

	Body mass index <25			Body mass index ≥25			P for heterogeneity
	Intake	No of cases	Model 2 HR (95% CI)	Intake	No of cases	Model 2 HR (95% CI)	
Total energy (kcal/d)							
Quartile 1	<1,625	74	1 (ref)	<1,636	55	1 (ref)	
Quartile 2	1,625-1,979	76	0.97 (0.70-1.34)	1,636-2,015	70	1.36 (0.95-1.96)	
Quartile 3	1,980-2,396	69	0.85 (0.61-1.20)	2,016-2,479	63	1.27 (0.87-1.86)	
Quartile 4	>2,396	90	1.09 (0.78-1.51)	>2,479	59	1.35 (0.90-2.02)	
P-trend			0.65			0.24	0.31
Carbohydrates (g/1000kcal*d)							
Quartile 1	<100.7	90	1 (ref)	<38.6	56	1 (ref)	
Quartile 2	100.7-112.4	86	1.18 (0.87-1.60)	38.6-43.4	63	1.16 (0.81-1.68)	
Quartile 3	112.5-123.9	73	1.12 (0.81-1.55)	43.5-48.3	63	1.19 (0.81-1.75)	
Quartile 4	>123.9	60	1.06 (0.75-1.51)	>48.3	65	1.35 (0.91-2.01)	
P-trend			0.70			0.15	0.17
Starch (g/1000kcal*d)							
Quartile 1	<48.6	97	1 (ref)	<47.1	49	1 (ref)	
Quartile 2	48.6-58.0	82	0.99 (0.73-1.34)	47.1-56.3	53	1.20 (0.81-1.77)	
Quartile 3	58.1-68.5	71	0.85 (0.62-1.16)	56.4-67.1	74	1.68 (1.15-2.44)	
Quartile 4	>68.5	59	0.65 (0.46-0.93)	>67.1	71	1.52 (1.02-2.28)	
P-trend			0.014			0.020	<0.001
Sugar (g/1000kcal*d)							
Quartile 1	<40.5	78	1 (ref)	<37.3	72	1 (ref)	
Quartile 2	40.5-49.9	70	0.94 (0.68-1.30)	37.3-46.8	54	0.71 (0.50-1.02)	
Quartile 3	50.0-60.6	79	1.18 (0.85-1.62)	46.9-58.0	68	0.95 (0.67-1.34)	
Quartile 4	>60.6	82	1.61 (1.16-2.24)	>58.0	53	0.76 (0.51-1.12)	
P-trend			0.002			0.34	0.005
Fiber (g/1000kcal*d)							
Quartile 1	<9.2	83	1 (ref)	<9.0	63	1 (ref)	
Quartile 2	9.2-10.9	84	0.96 (0.70-1.31)	9.0-10.8	51	0.71 (0.49-1.04)	
Quartile 3	11.0-13.1	81	1.11 (0.80-1.53)	10.9-12.9	78	1.10 (0.77-1.58)	
Quartile 4	>13.1	61	1.07 (0.74-1.53)	>12.9	55	0.77 (0.51-1.15)	
P-trend			0.58			0.50	0.24
Glycemic index (unit/d)							
Quartile 1	<53.7	109	1 (ref)	<53.5	61	1 (ref)	
Quartile 2	53.7-56.1	76	0.84 (0.63-1.13)	53.5-55.9	60	1.34 (0.93-1.93)	
Quartile 3	56.2-58.6	58	0.65 (0.46-0.90)	56.0-58.4	65	1.63 (1.13-2.35)	
Quartile 4	>58.6	66	0.64 (0.46-0.89)	>58.4	61	1.54 (1.05-2.28)	
P-trend			0.003			0.014	<0.001

	Body mass index <25			Body mass index 25			P for heterogeneity
	Intake	No of cases	Model 2 HR (95% CI)	Intake	No of cases	Model 2 HR (95% CI)	
Glycemic load (unit/1000kcal*d)							
Quartile 1	<55.6	79	1 (ref)	<95.7	71	1 (ref)	
Quartile 2	55.6-63.1	88	1.09 (0.81-1.47)	95.7-120.7	51	1.27 (0.88-1.83)	
Quartile 3	63.2-70.6	68	0.91 (0.66-1.27)	120.8-151.7	62	1.38 (0.95-2.01)	
Quartile 4	>70.6	74	0.97 (0.69-1.37)	>151.7	63	1.37 (0.92-2.04)	
P-trend			0.70			0.11	0.29

Model 2: Cox model stratified by center, age at baseline, and sex, and adjusted for BMI, total energy (as appropriate) and alcohol intake, smoking status, education, physical activity, and, in women menopausal status and type.