IJC
International Journal of Cancer

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

Raul Zamora-Ros[1], Sabina Rinaldi[1], Konstantinos K. Tsilidis[2,3], Elisabete Weiderpass[4,5,6,7], Marie-Christine Boutron-Ruault[8,9,10], Agnetha Linn Rostgaard-Hansen[11], Anne Tjønneland[11], Françoise Clavel-Chapelon[8,9,10], Sylvie Mesrine[8,9,10], Verena A. Katzke[12], Tilman Kühn[12], Jana Förster[13], Heiner Boeing[13], Antonia Trichopoulou[14,15,16], Pagona Lagiou[15,16,17], Eleni Klinaki[14], Giovanna Masala[18], Sabina Sieri[19], Fulvio Ricceri[20], Rosario Tumino[21], Amalia Mattiello[22], Petra H.M. Peeters[3,23], H. B(as) Bueno-de-Mesquita[3,24,25,26], Dagrun Engeset[27], Guri Skeie[28], Marcial Argüelles[29], Antonio Agudo[30], María-José Sánchez[31,32], María-Dolores Chirlaque[32,33], Aurelio Barricarte[32,34], Saioa Chamosa[35], Martin Almquist[36], Ada Tosovic[37], Joakim Hennings[38], Maria Sandström[39], Julie A Schmidt[40], Kay-Thee Khaw[41], Nicholas J. Wareham[42], Amanda J. Cross[3], Nadia Slimani[1], Graham Byrnes[1], Isabelle Romieu[1], Elio Riboli[3] and Silvia Franceschi[1]

[1] International Agency for Research on Cancer (IARC), Lyon, France
[2] Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
[3] School of Public Health, Imperial College London, London, United Kingdom
[4] Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
[5] Department of Etiological Cancer Research, Cancer Registry of Norway, Oslo, Norway
[6] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[7] Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland
[8] Inserm, Centre for Research in Epidemiology and Population Health (CESP), U1018, Nutrition, Hormones and Women's Health Team, Villejuif, France
[9] Université Paris Sud, UMRS 1018, Villejuif, France
[10] Institut Gustave Roussy, Villejuif, France
[11] Danish Cancer Society Research Center, Copenhagen, Denmark
[12] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[13] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany
[14] Hellenic Health Foundation, Athens, Greece
[15] Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece
[16] Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece
[17] Department of Epidemiology, Harvard School of Public Health, Boston, MA
[18] Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute – ISPO, Florence, Italy
[19] Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy
[20] Unit of Cancer Epidemiology - CERMS, Department of Medical Sciences, University of Turin and Città Della Salute E Della Scienza Hospital, Turin, Italy
[21] Cancer Registry and Histopathology Unit, "Civic M.P. Arezzo" Hospital, ASP Ragusa, Italy

Key words: macronutrients, total energy, glycemic index, differentiated thyroid carcinomas, EPIC

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; PUFA: polyunsaturated fats; TC: thyroid carcinoma

Additional Supporting Information may be found in the online version of this article.

Grant sponsor: The French National Cancer Institute (L'Institut National du Cancer INCA); **Grant number:** 2009–139; **Grant sponsors:** The European Commission: Public Health and Consumer Protection Directorate 1993 to 2004; Research Directorate-General 2005; Ligue contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid; German Cancer Research Center (DKFZ); German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health (RTICC (DR06/0020/0091); the participating regional governments from Asturias, Andalucía, Murcia, Navarra and Vasco Country; Catalan Institute of Oncology of Spain; Cancer Research UK; Medical Research Council, UK; the Hellenic Health Foundation; Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy; Compagnia San Paolo, Italy; Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Statistics Netherlands (The Netherlands); Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Nordforsk—Centre of Excellence Programme. Some authors are partners of ECNIS, a network of excellence of the 6FP of the EC.

DOI: 10.1002/ijc.29693

History: Received 31 Mar 2015; Accepted 25 June 2015; Online 17 July 2015

Correspondence to: Dr. Silvia Franceschi, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon, France, Tel.: +(33)−472738485, Fax: +(33)−472738575, E-mail: Franceschis@iarc.fr

What's new?

The role of lifestyle factors in the growing numbers of thyroid cancer remains unclear. Here, the authors uncover associations with high total energy intake and low consumption of polyunsaturated fatty acids in a large European cohort (EPIC). They further find positive associations with starch intake and glycemic index only in people with a body mass index equal or larger than 25, possibly implicating an altered insulin response in the etiology of this cancer.

[22] Dipartimento Di Medicina Clinica E Chirurgia, Federico II University, Naples, Italy
[23] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[24] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[25] Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands
[26] Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[27] The Norwegian Scientific Committee for Food Safety (VKM), Oslo, Norway
[28] Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway
[29] Public Health Directorate, Asturias, Spain
[30] Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology, Barcelona, Spain
[31] Escuela Andaluza De Salud Pública, Instituto De Investigación Biosanitaria (ibs.GRANADA), Hospitales Universitarios De Granada/Universidad De Granada, Granada, Spain
[32] CIBER Epidemiología Y Salud Pública (CIBERESP), Madrid, Spain
[33] Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain
[34] Public Health Institute of Navarra, Pamplona, Spain
[35] Public Health Division of Gipuzkoa, BioDonostia Research Institute, Health Department of Basque Region, San Sebastian
[36] Department of Surgery, University Hospital Lund, Lund, Sweden
[37] Department of Surgery, University Hospital Malmö, Malmö, Sweden
[38] Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden
[39] Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden
[40] Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom
[41] Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
[42] MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom

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 was to investigate the 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 ten European countries. Dietary data were collected using country-specific validated dietary questionnaires. Total carbohydrates, proteins, fats, saturated, monounsaturated and polyunsaturated fats (PUFA), starch, sugar, and fiber were computed as g/1,000 kcal. 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 found significant associations only with total energy ($HR_{Q4vs.Q1}$, 1.29; 95% CI, 1.00–1.68) and PUFA intakes ($HR_{Q4vs.Q1}$, 0.74; 95% CI, 0.57–0.95). However, the associations with starch and sugar intake and GI were significantly heterogeneous across body mass index (BMI) groups, *i.e.*, positive associations with starch and GI were found in participants with a BMI $\geq$ 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 $\geq$ 25 suggest that those persons may have a greater insulin response to high starch intake and GI than lean people.

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 in 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] macronutrients,[10] vitamins, microelements (iodine, nitrate and 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 this study was to evaluate prospectively the relationships among 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 multicenter, 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 ten 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 sociodemographic 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, 10th Revision, ICD-10*) during follow-up.

Of the 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 nonmelanoma skin cancer and 15,867 participants (including nine 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 this analysis. A total of 556 primary differentiated TC cases were retained for this 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/1,000 kcal) per day. GL was calculated as units/1,000 kcal per day, whereas GI was computed as units/day (because 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 (HRs) and 95% confidence intervals (CIs) 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/day) except when total energy is the main exposure and alcohol intake (g/day). In women, Model 2 also included menopause status, type of menopause (pre-, peri-, postmenopausal and surgical menopause).[7] Oral contraceptive use (yes, no and unknown) and history of

Table 1. Baseline characteristics of participants in the EPIC study by onset of differentiated thyroid carcinoma (TC) at follow-up and by 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 consumption (25–75%) (g/day)	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 (%)[1]				
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.

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/day). 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.* ≥ 25 kg/m^2), waist circumference (≤ 88 *vs.* >88 cm in women and ≤ 102 *vs.* >102 cm 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: (*i*) 67,378 women from the French component of EPIC (202 cases of differentiated TC), because French women represented the 40.5% of TC cases in women; (*ii*) 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 (*iii*) 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 two-tailed *p*-values <0.05 to be statistically significant. Statistical analyses were conducted using SAS, version 9.3, software (SAS Institute, Cary, NC).

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 perimenopausal or had undergone surgical menopause (Table 1).

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) 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/day)				
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/1,000 kcal day)				
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/1,000 kcal day)				
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/1,000 kcal day)				
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/1,000 kcal day)				
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/1,000 kcal day)				
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)
p-trend			0.72	0.44
Polyunsaturated fats (g/1,000 kcal day)				
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

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for differentiated thyroid cancer according to quartile of intake of total energy, macronutrients, glycemic index and load in the EPIC study (Continued)

		Thyroid carcinoma		
	Intake	No of cases	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Starch (g/1,000 kcal day)				
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/1,000 kcal day)				
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/1,000 kcal day)				
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/day)				
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/1,000 kcal day)				
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 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 ($HR_{Q4vs.Q1}$, 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 ($HR_{Q4vs.Q1}$, 0.74; 95% CI, 0.57–0.95; *p*-trend = 0.028; Table 2). In mutually adjusted models, results were similar to HRs observed in Model 2 but with wider 95% CI, especially for PUFA where the inverse associations became not significant ($HR_{Q4vs.Q1}$, 0.73; 95% CI, 0.49–1.08; *p*-trend = 0.15) (data not shown). 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 (Supporting Information Table S1).

The interactions between BMI group and the intake of starch, sugar and GI were statistically significant (*p*-values 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 ($HR_{Q4vs.Q1}$, 1.52; 95% CI, 1.02–2.28; *p*-trend = 0.020) and GI ($HR_{Q4vs.Q1}$, 1.54; 95% CI, 1.05–2.28; *p*-trend = 0.014) among participants with

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) 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			
	Intake	No of cases	Model 2, HR (95% CI)	Intake	No of cases	Model 2, HR (95% CI)	*p* for heterogeneity
Total energy (kcal/day)							
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/1,000 kcal day)							
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/1,000 kcal day)							
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/1,000 kcal day)							
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/1,000 kcal day)							
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/day)							
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
Glycemic load (unit/1,000 kcal day)							
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.

BMI $\geq$ 25. Conversely, in participants with BMI $<$ 25, starch intake ($HR_{Q4vs.Q1}$, 0.64; 95% CI, 046–0.89; p-trend = 0.003) and GI ($HR_{Q4vs.Q1}$, 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 ($HR_{Q4vs.Q1}$, 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 ($HR_{Q4vs.Q1}$, 4.15; 95% CI, 1.37–15.22; p-trend = 0.019; Supporting Information Table S1). 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 ($<$50 *vs.* $\geq$50 years), similar results as the entire cohort were found, highlighting the significant inverse association with PUFA in older subjects ($HR_{Q4vs.Q1}$, 0.63; 95% CI, 0.44–0.92; p-trend = 0.024; Supporting Information Table S1). No statistically significant interactions of dietary habits with smoking status or physical activity level were observed.

Results similar to those of Tables 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

This 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 $\geq$ 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 $\geq$ 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 Poland[26] showed higher intake of energy and carbohydrate-rich sources among TC cases as compared with 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 response[27] 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 $\geq$ 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 $\geq$ 25 compared with 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 have also been proposed as a causal link between abnormal glucose metabolism and cancer risk and doubling in insulin-like growth factor-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 an European cohort study, blood glucose level was associated with a significantly decreased risk of incident TC,[35] and no association between fasting serum insulin and TC in either 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 $\geq$ 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 this study include the prospective design, the completeness of follow-up and dietary questionnaire and the inclusion of participants from cohorts across ten 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 2 years of follow-up did not alter our findings. Patients with diabetes were not over-represented among TC cases, and, again, the exclusion of EPIC participants who were having diabetes 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 $\geq$25 encourages further study of the combined influence of diet, BMI, insulin resistance and related serum markers.

Acknowledgements

The authors thank Mr. Bertrand Hémon for his precious help with the EPIC database. The authors declare no conflict of interest.

References

1. Pellegriti G, Frasca F, Regalbuto C, et al. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol* 2013; 2013:965212.
2. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.
3. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995; 141: 259–77.
4. Franceschi S, Preston-Martin S, Dal Maso L, et al. A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* 1999; 10:583–95.
5. Rinaldi S, Lise M, Clavel-Chapelon F, et al. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* 2012; 131:E1004–14.
6. Zhao ZG, Guo XG, Ba CX, et al. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. *J Int Med Res* 2012; 40:2041–50.
7. Zamora-Ros R, Rinaldi S, Biessy C, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. *In J Cancer* 2015; 136:1218–27.
8. Dal Maso L, Bosetti C, La Vecchia C, et al. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. *Cancer Causes Control* 2009; 20:75–86.
9. Choi WJ, Kim J. Dietary factors and the risk of thyroid cancer: a review. *Clin Nutr Res* 2014; 3:75–88.
10. Marcello MA, Sampaio AC, Geloneze B, et al. Obesity and excess protein and carbohydrate consumption are risk factors for thyroid cancer. *Nutr Cancer* 2012; 64:1190–5.
11. Zhang LR, Sawka AM, Adams L, et al. Vitamin and mineral supplements and thyroid cancer: a systematic review. *Eur J Cancer Prev* 2013; 22:158–68.
12. Kilfoy BA, Zhang Y, Park Y, et al. Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study. *Int J Cancer* 2011; 129:160–72.
13. Xiao Q, Park Y, Hollenbeck AR, et al. Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP Diet and Health Study. *Cancer Epidemiol Biomarkers Prev* 2014; 23:1102–8.
14. Randi G, Ferraroni M, Talamini R, et al. Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol* 2008; 19:380–3.
15. Clero E, Doyon F, Chungue V, et al. Dietary patterns, goitrogenic food, and thyroid cancer: a case–control study in French Polynesia. *Nutr Cancer* 2012; 64:929–36.
16. Markaki I, Linos D, Linos A. The influence of dietary patterns on the development of thyroid cancer. *Eur J Cancer* 2003; 39:1912–9.
17. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997; 26:S6–14.
18. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002; 5:1113–24.
19. Margetts BM, Pietinen P. European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. *Int J Epidemiol* 1997; 26:S1–5.
20. Slimani N, Deharveng G, Unwin I, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* 2007; 61:1037–56.
21. van Bakel MM, Kaaks R, Feskens EJ, et al. Dietary glycaemic index and glycaemic load in the European Prospective Investigation into Cancer and Nutrition. *Eur J Clin Nutr* 2009; 63:S188–205.
22. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr* 2003; 6:407–13.
23. Ferrari P, Slimani N, Ciampi A, et al. Evaluation of under- and overreporting of energy intake in the 24-hour diet recalls in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* 2002; 5:1329–45.
24. Franceschi S, Vaccarella S. Thyroid cancer: an epidemic of disease or an epidemic of diagnosis? *Int J Cancer* 2015; 136:2738–9.
25. Chatenoud L, La Vecchia C, Franceschi S, et al. Refined-cereal intake and risk of selected cancers in Italy. *Am J Clin Nutr* 1999; 70:1107–10.
26. Przybylik-Mazurek E, Hubalewska-Dydejczyk A, Kuzniarz-Rymarz S, et al. Dietary patterns as risk factors of differentiated thyroid carcinoma. *Postepy Hig Med Dosw (Online)* 2012; 66:11–5.
27. Gnagnarella P, Gandini S, La Vecchia C, et al. Glycemic index, glycemic load, and cancer risk: a meta-analysis. *Am J Clin Nutr* 2008; 87:1793–801.
28. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 2002; 11:1531–43.
29. Bae MJ, Kim SS, Kim WJ, et al. High prevalence of papillary thyroid cancer in Korean women with insulin resistance. *Head Neck*, in press, doi:10.1002/hed.23848.
30. Shih SR, Chiu WY, Chang TC, et al. Diabetes and thyroid cancer risk: literature review. *Exp Diabetes Res* 2012; 2012:578285.
31. Schmidt JA, Allen NE, Almquist M, et al. Insulin-like growth factor-I and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2014; 23:976–85.
32. Yeo Y, Ma SH, Hwang Y, et al. Diabetes mellitus and risk of thyroid cancer: a meta-analysis. *PLoS One* 2014; 9:e98135.
33. Guo H, Sun M, He W, et al. The prevalence of thyroid nodules and its relationship with metabolic parameters in a Chinese community-based population aged over 40 years. *Endocrine* 2014; 45:230–5.
34. Bi Y, Lu J, Wang W, et al. Cohort profile: risk evaluation of cancers in Chinese diabetic individuals: a longitudinal (REACTION) study. *J Diabetes* 2014; 6:147–57.
35. Almquist M, Johansen D, Björge T, et al. Metabolic factors and risk of thyroid cancer in the Metabolic Syndrome and Cancer Project (Me-Can). *Cancer Causes Control* 2011; 22:743–51.
36. Han JM, Kim TY, Jeon MJ, et al. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. *Eur J Endocrinol* 2013; 168:879–86.
37. Willett W. Nutritional epidemiology. New York: Oxford University Press, 1998.
38. Berg JP, Glattre E, Haldorsen T, et al. Long-chain serum fatty acids and risk of thyroid cancer: a population-based case–control study in Norway. *Cancer Causes Control* 1994; 5:433–9.
39. Kim KM, Jung BH, Lho DS, et al. Alteration of urinary profiles of endogenous steroids and polyunsaturated fatty acids in thyroid cancer. *Cancer Lett* 2003; 202:173–9.
40. Das SC, Isichei UP. Serum and thyroid tissue lipids in patients with thyroid tumors in euthyroidism. *Indian J Exp Biol* 1989; 27:538–44.
41. Linseisen J, Welch AA, Ocke M, et al. Dietary fat intake in the European Prospective Investigation into Cancer and Nutrition: results from the 24-h dietary recalls. *Eur J Clin Nutr* 2009; 63:S61–S80.
42. Bosetti C, Kolonel L, Negri E, et al. A pooled analysis of case–control studies of thyroid cancer. VI. Fish and shellfish consumption. *Cancer Causes Control* 2001; 12:375–82.