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Consumption of Fish Is Not Associated with Risk of Differentiated Thyroid Carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study

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Abstract

Background: Differentiated thyroid cancer (TC) is the most common endocrine cancer. Fish can be an important source of iodine and other micronutrients and contaminants that may affect the thyroid gland and TC risk.

Objective: We prospectively evaluated the relations between the consumption of total fish and different fish types and shellfish and TC risk in the EPIC (European Prospective Investigation into Cancer and Nutrition) study.

Methods: EPIC is a cohort of >500,000 men and women, mostly aged 35–70 y, who were recruited in 10 European countries. After a mean follow-up of 14 y, 748 primary differentiated TC cases were diagnosed; 666 were in women and

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601 were papillary TC. Data on intakes of lean fish, fatty fish, fish products, and shellfish were collected by using country-specific validated dietary questionnaires at recruitment. Multivariable Cox regression was used to calculate HRs and 95% CIs adjusted for many potential confounders, including dietary and nondietary factors.

Results: No significant association was observed between total fish consumption and differentiated TC risk for the highest compared with the lowest quartile (HR: 1.03; 95% CI: 0.81, 1.32; *P*-trend = 0.67). Likewise, no significant association was observed with the intake of any specific type of fish, fish product, or shellfish. No significant heterogeneity was found by TC subtype (papillary or follicular tumors), by sex, or between countries with low and high TC incidence.

Conclusion: This large study shows that the intake of fish and shellfish was not associated with differentiated TC risk in Europe, a region in which iodine deficiency or excess is rare. *J Nutr* 2017;147:1366–73.

Keywords: thyroid cancer, fish, intake, cohort, EPIC

Introduction

Approximately 230,000 new cases of thyroid cancer (TC) were estimated in 2012 among women and 70,000 among men worldwide, with a large variability in incidence rates in different parts of the world (1). The traditional classification of TC is based on morphologic and clinical features: differentiated [including papillary (~80% of all TC cases) and follicular (10–20%) tumors], medullary (5–10%), anaplastic tumors (<5%), and other rare tumors (e.g., thyroid lymphoma and sarcoma) (2).

To date, the only 3 well-established risk factors for TC are exposure to ionizing radiation (3), previous benign thyroid hyperplasia (including goiter and thyroid nodules) (4), and high body mass (5, 6). Among dietary exposures (7–9), potential associations with TC have been suggested with intakes of iodine-rich seafood (10, 11), goitrogenic vegetables (12, 13), PUFAs (14), and alcohol (15).

Fish and fish products are considered healthy foods in several dietary patterns [e.g., Mediterranean diet (16), traditional Japanese diet (17), and Healthy Nordic Food Index (18)], because they are rich in essential nutrients, such as protein of high biological value and minerals (e.g., iodine, calcium, iron, and zinc) (19, 20). Fatty fish are also a good source of n–3 PUFAs (EPA and DHA) and lipid-soluble vitamins (retinol, vitamin D, and vitamin E). However, fish can also contain some contaminants such as toxic heavy metals and polychlorinated biphenyls (PCBs) (21–23).

A current review found no association between fish consumption and TC risk in data from a pooled analysis of 15 case-control studies (5) and 1 US-based cohort (24). However, further prospective studies, in larger number of cases, are needed to investigate the associations between the intakes of fish and fish subtypes and TC etiology, especially by subtypes of TC. The aim of the current study was to prospectively evaluate the relations between the consumption of total fish, and fish subtypes and the risk of developing differentiated TC in the EPIC (European Prospective Investigation into Cancer and Nutrition) study. EPIC is one of the largest cohorts worldwide, with a large number of differentiated TC cases and substantial heterogeneity in fish consumption among participants from 10 European countries (19) and therefore constitutes an ideal setting to investigate this association.

Methods

Study population. EPIC is a multicenter cohort that was designed to principally investigate the role of dietary, environmental, and genetic factors in the risk of developing cancer. This cohort has 23 centers located in 10 European countries: Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands, and the United Kingdom. Briefly, the EPIC cohort includes 521,324 participants (70.1% women), mostly aged between 35 and 70 y, recruited between 1992 and 2000, primarily from the general population, with the exception of France (women who were health insurance members), Utrecht and Florence (women attending breast cancer screening), Oxford (mostly health-conscious volunteers including a large proportion of vegetarians), and some centers in Spain and Italy (where the participants were mostly blood donors) (25). All of the participants gave written informed consent, and the project was approved by ethics review boards of the International Agency for Research on Cancer and the local participating centers.

Dietary and lifestyle data. At baseline, dietary data were collected with different dietary assessment instruments (e.g., quantitative or semiquantitative FFQs, diet histories, or a dietary questionnaire combined with a 7-d food record) that were developed and locally validated in EPIC previously (25, 26). Face-to-face interviews were conducted in Greece, Ragusa and Naples (Italy), and Spain, whereas questionnaires were

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Supplemental Table 1 is available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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Abbreviations used: EPIC, European Prospective Investigation into Cancer and Nutrition; PCB, polychlorinated biphenyl; TC, thyroid cancer.

self-administered in all other centers. Total energy and nutrient intakes were estimated by using the dietary questionnaires and the standardized EPIC Nutrient Database (27).

For the current analysis, we used the following categories of fish and shellfish intake: lean fish and lean fish product intake [e.g., cod, haddock, and plaice (fat content ≤4 g/100 g)], fatty fish and fatty fish product intake [e.g., salmon, tuna, and trout (fat content between 4 and 14 g/100 g)], fish and fish product intake (sum of lean and fatty fish and fish products), shellfish intake (including seafood such as prawn, crab, and mussels), and total fish and shellfish intake, which was defined as the sum of intakes of fish, fish products, and shellfish (19).

Information on sociodemographic and lifestyle characteristics, such as educational level, tobacco and alcohol consumption, physical activity, and medical history, was self-reported at recruitment through standardized questionnaires (25). At baseline, anthropometric data were measured by trained staff in all centers, except in Oxford (United Kingdom), Norway, and France, where self-reported data were obtained.

Follow-up and case ascertainment. Incident cancer cases were identified through population-based cancer registries or active follow-up (directly from study participants or next of kin) and confirmed by a combination of methods including health insurance records and cancer and pathology registries, depending on the center. Complete follow-up censoring dates varied among centers, ranging between December 2010 and December 2014. Cases were defined as participants with a first primary TC (code C73 according to the International Classification of Diseases, 10th Revision) during follow-up.

Of the 857 TC cases, anaplastic (n = 9), medullary (n = 37), and TC defined as lymphoma (n = 1) or "other morphologies" (n = 5) were excluded. We also excluded 29,332 participants (including 45 differentiated TC cases) with missing or null follow-up time or prevalent cancer other than nonmelanomatous skin cancer, 1277 participants with incomplete information on lifestyle, and 14,555 participants (including 12 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). A total of 476,108 men and women and 6,639,459 person-years of observation (mean follow-up time of 14.0 y) were included in this analysis. In this study, we had a total of 748 primary differentiated TC cases, including 601 papillary, 109 follicular, and 38 not-otherwise-specified TC, most likely to also be papillary TC.

Statistical analyses. Cox proportional hazard models were used to estimate HRs and 95% CIs for the association between fish intake and TC risk. Age was used as the underlying primary dependent time variable, with entry time defined as the participant's age at recruitment and exit time as age at TC diagnosis, death, or censoring date (lost to or end of follow-up), whichever occurred first. Tests and graphs based on Schoenfeld residuals were used to assess proportional hazards assumptions, which were satisfied. Model 1 was stratified by center, age at baseline (1-y interval), and sex. Model 2 was additionally adjusted for the following potential confounders: BMI, smoking status, educational level, physical activity, and total energy and alcohol intakes. In women, model 2 was also adjusted for menopausal status and type, oral contraceptive use, and infertility problems, because these were TC risk factors in this study (28). Because fish is a source of iodine and contaminants, absolute fish intakes could be as important as intakes adjusted for total energy. We conducted model 2 with and without adjustment for total energy and the results were identical; therefore, we only present the results including total energy in model 2.

The intake of fish, overall and by fish type, was assessed by cohort-wide quartiles or BMI-, age-, or sex-specific quartile in stratified analyses. For shellfish consumption, because of the high number of nonconsumers (33.6%), instead of quartiles, 3 groups were created: nonconsumers and those below and above the median of consumers. Tests for linear trend were performed by assigning the median of each quartile as scores. Fish and shellfish consumption was also evaluated as a continuous variable per 10 and 1 g/d, respectively. Possible interactions with sex, smoking status (never, former, or current smokers), alcohol intake (0, >0–15, >15–29.9, or ≥30 g/d), physical activity (inactive, active, or unknown, according to the Cambridge Physical Activity Index) (29), and BMI (in kg/m^2; <25 or ≥25) were examined by including the interaction terms in the most-adjusted models. Separate sex-specific models were fitted, because borderline significant heterogeneity between sex and total fish and shellfish consumption and differentiated TC risk was detected. Similar models were defined to assess the risk of TC by subtype (papillary and follicular). Separate models were also computed to check the variability between countries with a high compared with low TC incidence. EPIC countries with TC incidence rates of >5/10,000 in women (i.e., France, Germany, Greece, Italy, and Spain) were considered to have high TC incidence. The Wald test was used to evaluate the heterogeneity of risk between sexes and TC subtypes. Two types of sensitivity analyses were performed by excluding the following participants from the analyses: *1*) 67,391 women from the French component of EPIC (248 cases of differentiated TC), because French women represented 37.2% of TC cases in women, and *2*) 77 cases who were diagnosed with TC within the first 2 y of follow-up, because some participants may have modified their diet during the early prediagnostic period of the disease.

Calibration of dietary data. A single 24-h dietary recall was also taken from an 8% random sample of the cohort (36,994 participants) by using a detailed computerized 24-h recall method (30) to calibrate dietary measurements of fish, fish products, and shellfish intake across countries and to correct for systematic overestimation or underestimation of dietary intakes (31). The 24-h recall estimates for fish, fish products, and shellfish of the participants with these data were regressed on the values for these foods estimated from the main dietary questionnaire values. Age at recruitment, center, and total energy intake were included as covariates; and data were weighted by day of the week and season of the year during which the 24-h recall was collected. Zero consumption values in the main dietary questionnaires were excluded in the regression calibration models, and a 0 was directly imputed as a corrected value. Country- and sex-specific calibration models were used to obtain individual predicted values of dietary exposure for all participants. Cox regression models were then conducted by using the predicted (calibrated) values for each individual on a continuous scale. The SE of the calibrated coefficient was estimated with bootstrap sampling in the calibration and disease models and repeated 300 times (31). P values <0.05 were considered significant. Statistical analyses were conducted by using SAS, version 9.3, software (SAS Institute).

Results

In our study, women represented 70.1% of the total population and the vast majority of differentiated TC cases (89.0%). Differentiated TC was ~3 times more common in women than in men. The most common subtype of differentiated TC was papillary (80.3%), followed by follicular (14.6%) and not otherwise specified (5.1%) for both sexes (**Table 1**). The median intake of total fish and shellfish in men (27.7 g/d) and women (28.0 g/d) was similar. The highest consumption of total fish and shellfish in men and women was in Spain and Norway, respectively.

Overall, men and women in the highest quartile of total fish and shellfish intake were older and more physically active, had a higher BMI and waist circumference, reported a higher total energy intake, were more likely to be a current smoker and to have a secondary education, and had a higher prevalence of diabetes than those in the lowest quartile (**Supplemental Table 1**). Women in the highest fish-intake quartile reported more infertility problems than did those in the bottom quartile (Supplemental Table 1).

No significant association was observed between total fish consumption and differentiated TC risk for the highest

TABLE 1 Number of differentiated thyroid cancer cases and medians (25th–75th percentiles) of total fish and shellfish intake by sex and country in the EPIC study[1]

	Women (*n* = 333,876)						Men (*n* = 142,232)					
		Cancer cases, *n*						Cancer cases, *n*				
Country	All, *n*	Thyroid	Papillary	Follicular	NOS	Total fish and shellfish intake, g/d	All, *n*	Thyroid	Papillary	Follicular	NOS	Total fish and shellfish intake, g/d
Denmark	28,714	26	18	8	0	36.0 (24.2–51.5)	26,291	13	10	3	0	42.6 (28.6–60.9)
France[2]	67,391	248	227	19	2	31.0 (18.6–49.7)	—	—	—	—	—	—
Germany	27,373	67	47	18	2	15.8 (7.0–25.6)	21,178	15	11	3	1	20.5 (9.8–31.2)
Greece	15,229	28	22	1	5	18.3 (12.6–27.1)	10,815	8	6	0	2	20.7 (13.6–32.2)
Italy	30,511	106	81	16	9	24.9 (14.2–40.6)	14,032	21	16	3	2	24.9 (14.4–38.5)
Norway[2]	33,972	36	31	4	1	79.7 (53.0–115.6)	—	—	—	—	—	—
Spain	24,846	74	62	11	1	47.1 (29.3–70.8)	15,138	6	4	2	0	68.7 (43.1–101.6)
Sweden	26,365	29	20	4	5	21.7 (10.9–39.4)	22,301	10	5	3	2	20.8 (10.4–41.6)
Netherlands	26,910	13	10	3	0	8.1 (3.3–15.6)	9627	4	2	1	1	8.3 (3.8–15.5)
United Kingdom	52,565	39	24	10	5	26.1 (0–43.6)	22,850	5	5	0	0	26.5 (8.0–42.5)
Total	333,876	666	542	94	30	28.0 (13.7–50.0)	142,232	82	59	15	8	27.7 (13.8–48.5)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; NOS, not otherwise specified.

[2] Only women were recruited in France and Norway.

compared with the lowest quartile in either model 1 (HR: 1.03; 95% CI: 0.81, 1.32; *P*-trend = 0.67) or the multivariable model 2 (HR: 1.05; 95% CI: 0.81, 1.34; *P*-trend = 0.62) analysis (**Table 2**). No significant association was found with total intakes of fish and fish products or with lean fish, fatty fish, or shellfish separately. Separate analyses of papillary or follicular TC also showed no significant associations with the intake of any type of fish or shellfish, and no evidence of heterogeneity in findings by TC histologic subtypes.

A borderline significant interaction in the association between the intake of total fish and differentiated TC risk with sex was found (*P*-interaction = 0.07), and therefore results divided by sex are presented (**Table 3**). In women, no significant association with total fish or fish subtypes was observed. In men, a borderline significant inverse trend between total fish and shellfish intake and differentiated TC risk was detected according to model 2 (*P*-trend = 0.05), although the associations for the observed continuous variable (HR: 0.95; 95% CI: 0.87, 1.05), the calibrated continuous variable (HR: 0.95; 95% CI: 0.81, 1.11) (Table 3), or the extreme quartiles (HR: 0.43; 95% CI: 0.17, 1.05; with a low number of TC cases, e.g., 9 cases in the fourth quartile) were null (data not shown). No significant interaction was observed with BMI status, smoking status, physical activity, or educational level (*P*-interaction = 0.12, 0.81, 0.45, and 0.73, respectively). A similar lack of heterogeneity was observed in the association of fish intake with TC risk between countries with low and high TC incidence rates (**Table 4**). In the sensitivity analyses that excluded either the large French EPIC component or TC cases who had been diagnosed within the first 2 y of follow-up, the results for any fish intake and TC risk were almost identical to those of the entire cohort (data not shown).

Discussion

In the current study, the largest prospective investigation so far on fish intake and differentiated TC risk to our knowledge, no associations with total fish or shellfish intake were observed. The lack of associations is especially convincing for papillary carcinomas and women, which represented the vast majority of TC cases in EPIC. The intake of fish and shellfish was also unrelated to TC risk in all follicular TC and in both low- and high-TC-incidence countries.

Our results are in concordance with the previous cohort study (24), a systematic review (5), a meta-analysis (8), and a pooled analysis of case-control studies from the United States, Europe, Japan, and China (11). However, a high fish intake was associated with a significantly lower risk of TC (OR: 0.65; 95% CI: 0.48, 0.88) in studies conducted in areas with a history of goiter endemicity, such as Italy and certain parts of Sweden (11). A few additional small case-control studies suggested a protective association between fish and shellfish consumption and TC risk (10, 13, 32).

Saltwater fish and shellfish are a rich source of iodine, which is known to play a role in the onset of goiter (33). However, the possible association with TC risk is complex. A bimodal risk effect of iodine on the pathogenesis of TC has been suspected for a long time (11) and was recently shown in a study from South Korea (34) in which both insufficient and extremely high iodine intakes were associated with an increased risk of benign nodules and TC (97.5% papillary tumors). A Danish ecological study evaluated the incidence before and after iodine supplementation and found that the incidence of TC increased after supplementation with iodine (35). This trend can, however, be explained by the increased ability to detect thyroid nodules and TC after the introduction of ultrasonography (36). The lack of influence of iodine from fish is not surprising because there are currently few mildly iodine-deficient areas in Europe and iodized salt is widely available (37). Likewise, extremely high iodine intakes, like those reported in Japan and other Pacific countries where the intake of seafood and seaweeds is high, are very rare in Europe (10).

Fatty fish is a rich source of PUFAs, particularly n–3 PUFAs (EPA and DHA), that have anti-inflammatory properties through their impact on prostaglandin synthesis and have been observed to be a protective factor in some types of cancers (38), possibly including TC (21, 39). A study of long-chain serum FAs and the risk of TC in Norway (40) showed an inverse association between combinations of arachidonic acid (20:4n−6), EPA, and DHA serum concentrations and the risk of developing papillary TC. A similar inverse association between PUFA intake and TC risk was reported in the EPIC study (14). The protection, however, may derive from food sources other than fish (e.g., vegetable oils and nuts).

TABLE 2 HRs (95% CIs) for differentiated TC and subtypes, according to quartile of intake of total fish and shellfish and subtypes in the EPIC study[1]

		Differentiated TC			Papillary TC			Follicular TC			
	Intake, g/d	Cases, *n*	Model 1	Model 2	Cases, *n*	Model 1	Model 2	Cases, *n*	Model 1	Model 2	*P*-heterogeneity
Total fish and shellfish											
Quartile 1	<13.7	158	1 (ref)	1 (ref)	124	1 (ref)	1 (ref)	26	1 (ref)	1 (ref)	
Quartile 2	13.7–27.9	196	0.98 (0.79, 1.22)	0.99 (0.80, 1.23)	161	1.01 (0.78, 1.27)	1.03 (0.78, 1.27)	27	0.90 (0.52, 1.57)	0.92 (0.52, 1.60)	
Quartile 3	28.0–49.7	216	1.21 (0.90, 1.39)	1.13 (0.90, 1.41)	168	1.06 (0.83, 1.36)	1.06 (0.83, 1.36)	32	1.11 (0.63, 1.95)	1.17 (0.66, 2.06)	
Quartile 4	>49.7	178	1.03 (0.81, 1.32)	1.05 (0.81, 1.34)	148	1.04 (0.79, 1.36)	1.03 (0.78, 1.36)	24	0.97 (0.51, 1.84)	1.03 (0.53, 1.99)	
P-trend			0.67	0.62		0.73	0.79		0.97	0.81	
Observed continuous (by 10 g/d)			1.00 (0.98, 1.03)	1.00 (0.98, 1.03)		1.01 (0.98, 1.39)	1.01 (0.98, 1.03)		0.97 (0.90, 1.05)	0.98 (0.90, 1.06)	
Calibrated continuous (by 10 g/d)			1.02 (0.95, 1.09)	1.01 (0.95, 1.08)		1.04 (0.96, 1.11)	1.03 (0.96, 1.11)		0.92 (0.76, 1.10)	0.92 (0.76, 1.10)	0.17
Fish + fish products											
Quartile 1	<12.2	156	1 (ref)	1 (ref)	121	1 (ref)	(ref) 1	27	1 (ref)	1 (ref)	
Quartile 2	12.3–24.8	195	0.94 (0.75, 1.17)	0.95 (0.76, 1.18)	153	0.91 (0.71, 1.17)	0.91 (0.71, 1.17)	31	0.98 (0.57, 1.67)	0.99 (0.58, 1.70)	
Quartile 3	24.9–44.2	214	1.06 (0.85, 1.32)	1.07 (0.85, 1.33)	175	1.06 (0.82, 1.36)	1.06 (0.82, 1.36)	26	0.82 (0.46, 1.47)	0.86 (0.48, 1.54)	
Quartile 4	>44.2	183	1.08 (0.84, 1.38)	1.09 (0.85, 1.39)	152	1.09 (0.83, 1.43)	1.08 (0.82, 1.43)	25	0.92 (0.49, 1.74)	0.97 (0.51, 1.86)	
P-trend			0.33	0.32		0.27	0.32		0.78	0.91	
Observed continuous (by 10 g/d)			1.01 (0.98, 1.03)	1.01 (0.98, 1.04)		1.01 (0.98, 1.04)	1.01 (0.98, 1.04)		0.96 (0.89, 1.05)	0.97 (0.89, 1.05)	
Calibrated continuous (by 10 g/d)			1.03 (0.95, 1.10)	1.02 (0.95, 1.10)		1.05 (0.97, 1.14)	1.05 (0.97, 1.14)		0.97 (0.89, 1.05)	0.91 (0.76, 1.11)	0.13
Lean fish + lean fish products											
Quartile 1	<1.6	186	1 (ref)	1 (ref)	147	1 (ref)	1 (ref)	32	1 (ref)	1 (ref)	
Quartile 2	1.6–10.1	202	1.18 (0.95, 1.47)	1.18 (0.95, 1.47)	156	1.14 (0.89, 1.45)	1.14 (0.89, 1.45)	32	1.14 (0.66, 1.97)	1.15 (0.67, 2.00)	
Quartile 3	10.2–21.9	175	1.09 (0.86, 1.37)	1.09 (0.86, 1.37)	150	1.14 (0.88, 1.47)	1.14 (0.88, 1.47)	18	0.74 (0.38, 1.45)	0.76 (0.39, 1.50)	
Quartile 4	>21.9	185	1.23 (0.96, 1.57)	1.22 (0.96, 1.56)	148	1.18 (0.90, 1.55)	1.17 (0.89, 1.54)	27	1.24 (0.64, 2.37)	1.25 (0.64, 2.41)	
P-trend			0.19	0.21		0.31	0.37		0.56	0.55	
Observed continuous (by 10 g/d)			1.01 (0.97, 1.05)	1.00 (0.96, 1.05)		1.01 (0.96, 1.05)	1.01 (0.96, 1.05)		1.00 (0.89, 1.12)	1.00 (0.89, 1.12)	
Calibrated continuous (by 10 g/d)			1.03 (0.94, 1.12)	1.02 (0.93, 1.12)		1.03 (0.94, 1.14)	1.03 (0.93, 1.14)		0.96 (0.75, 1.23)	0.95 (0.75, 1.21)	0.48
Fatty fish + fatty fish products											
Quartile 1	<1.6	144	1 (ref)	1 (ref)	115	1 (ref)	1 (ref)	23	1 (ref)	1 (ref)	
Quartile 2	1.6–7.8	240	1.07 (0.86, 1.33)	1.08 (0.87, 1.34)	191	1.01 (0.79, 1.28)	1.01 (0.79, 1.29)	34	1.20 (0.69, 2.09)	1.23 (0.71, 2.15)	
Quartile 3	7.9–16.0	181	0.97 (0.77, 1.22)	0.98 (0.78, 1.24)	146	0.92 (0.71, 1.19)	0.92 (0.71, 1.19)	26	1.08 (0.59, 1.98)	1.14 (0.62, 2.08)	
Quartile 4	>16.0	183	1.04 (0.82, 1.32)	1.06 (0.83, 1.34)	149	1.01 (0.78, 1.32)	1.02 (0.78, 1.33)	26	1.03 (0.55, 1.92)	1.10 (0.59, 2.07)	
P-trend			0.88	0.88		0.87	0.89		0.87	0.98	
Observed continuous (by 10 g/d)			0.99 (0.93, 1.05)	0.99 (0.93, 1.05)		1.01 (0.95, 1.08)	1.01 (0.95, 1.08)		0.86 (0.71, 1.04)	0.87 (0.72, 1.05)	
Calibrated continuous (by 10 g/d)			1.01 (0.89, 1.14)	1.01 (0.90, 1.14)		1.04 (0.91, 1.19)	1.04 (0.91, 1.19)		0.86 (0.64, 1.16)	0.88 (0.65, 1.19)	0.20
Shellfish											
Group 1	0.8	291	1 (ref)	1 (ref)	238	1 (ref)	1 (ref)	41	1 (ref)	1 (ref)	
Group 2	>0.8–4.1	209	0.93 (0.76, 1.14)	0.94 (0.75, 1.17)	169	0.95 (0.75, 1.21)	0.97 (0.76, 1.23)	29	1.07 (0.55, 2.07)	1.11 (0.57, 2.15)	
Group 3	>4.1	248	1.15 (0.93, 1.43)	0.87 (0.71, 1.07)	194	0.82 (0.66, 1.02)	0.84 (0.67, 1.04)	39	1.32 (0.73, 2.38)	1.42 (0.78, 2.59)	
P-trend			0.31	0.41		0.14	0.16		0.51	0.41	
Observed continuous (by 1 g/d)			0.99 (0.97, 1.00)	0.99 (0.98, 1.00)		0.98 (0.97, 1.00)	0.99 (0.97, 1.00)		1.00 (0.97, 1.04)	1.03 (0.98, 1.04)	
Calibrated continuous (by 1 g/d)			0.99 (0.97, 1.01)	0.99 (0.97, 1.01)		0.98 (0.96, 1.00)	0.98 (0.96, 1.00)		1.03 (0.96, 1.10)	1.03 (0.96, 1.10)	0.17

[1] Model 1 was stratified by center, age at baseline (1-y interval), and sex. Model 2 was additionally adjusted for BMI, smoking status, educational level, physical activity, and total energy and alcohol intakes and, in women, also adjusted for menopausal status and type, oral contraceptive use, and infertility problems. EPIC, European Prospective Investigation into Cancer and Nutrition; ref, reference; TC, thyroid cancer.

TABLE 3 HRs (95% CIs) for differentiated TC stratified by sex according to intake of total fish and shellfish and subtypes in the EPIC study[1]

	Women (666 TC cases)		Men (82 TC cases)		
	Model 1	Model 2	Model 1	Model 2	*P*-heterogeneity
Total fish and shellfish (by 10 g/d)					
Observed	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	0.94 (0.85, 1.03)	0.95 (0.87, 1.05)	
Calibrated	1.03 (0.96, 1.11)	1.03 (0.96, 1.11)	0.95 (0.81, 1.11)	0.95 (0.81, 1.11)	0.30
Fish + fish products (by 10 g/d)					
Observed	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	0.96 (0.87, 1.05)	0.97 (0.88, 1.07)	
Calibrated	1.04 (0.96, 1.13)	1.04 (0.95, 1.13)	0.97 (0.82, 1.14)	0.97 (0.82, 1.14)	0.42
Lean fish + lean fish products (by 10 g/d)					
Observed	1.01 (0.97, 1.06)	1.01 (0.97, 1.05)	0.93 (0.79, 1.11)	0.95 (0.80, 1.12)	
Calibrated	1.04 (0.94, 1.15)	1.03 (0.94, 1.14)	0.93 (0.72, 1.21)	0.94 (0.72, 1.22)	0.41
Fatty fish + fatty fish products (by 10 g/d)					
Observed	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)	0.97 (0.82, 1.15)	0.99 (0.85, 1.16)	
Calibrated	0.96 (0.84, 1.11)	0.96 (0.84, 1.11)	1.12 (0.93, 1.35)	1.12 (0.93, 1.34)	0.20
Shellfish (by 1 g/d)					
Observed	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.94 (0.87, 1.01)	0.94 (0.88, 1.01)	
Calibrated	0.99 (0.87, 1.10)	0.99 (0.87, 1.01)	0.97 (0.91, 1.03)	0.97 (0.91, 1.04)	0.56

[1] Model 1 was stratified by center and age at baseline (1-y interval). Model 2 was additionally adjusted for BMI, smoking status, educational level, physical activity, and total energy and alcohol intakes and, in women, also adjusted for menopausal status and type, oral contraceptive use, and infertility problems. EPIC, European Prospective Investigation into Cancer and Nutrition; TC, thyroid cancer.

Fish can also contain different amounts of metals, such as copper and cobalt and toxic heavy metals such as arsenic, molybdenum, lead, mercury, and cadmium (41, 42), and of PCBs (39). A study on trace elements suggested that an excess in the concentrations of heavy metals (mercury, cobalt, and iodine) and low serum concentrations of selenium increase the frequency of goiter and TC (43). In addition, a Korean study suggested that the accumulation of cadmium in thyroid tissue may be an important etiologic factor of TC progression and aggravation in Korean women (44). Fish consumption, with possible PCB contamination, did not appear to increase TC risk in New York anglers (39). Given the absence of association, the role of any of these contaminants is unlikely to be relevant in the population studied.

The strengths of this study are its prospective design, the inclusion of a large number of TC cases, and the use of country-specific validated dietary questionnaires in a study that showed substantial variations in fish intakes across centers (26). The influence of prevalent TC on the null associations is unlikely, because the exclusion of cases diagnosed within the first 2 y of

TABLE 4 HRs (95% CIs) for differentiated TC according to the intake of total fish and shellfish and subtypes by high- and low-TC-incidence countries in the EPIC study[1]

	Low-TC-incidence countries (175 TC cases)		High-TC-incidence countries[2] (573 TC cases)		
	Model 1	Model 2	Model 1	Model 2	*P*-heterogeneity
Total fish and shellfish (by 10 g/d)					
Observed	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)	
Calibrated	0.97 (0.88, 1.08)	0.97 (0.88, 1.08)	1.05 (0.96, 1.15)	1.05 (0.96, 1.15)	0.27
Fish + fish products (by 10 g/d)					
Observed	1.00 (0.96, 1.04)	0.99 (0.96, 1.04)	1.03 (0.99, 1.07)	1.03 (0.99, 1.07)	
Calibrated	0.98 (0.89, 1.09)	0.98 (0.89, 1.08)	1.08 (0.97, 1.20)	1.07 (0.97, 1.19)	0.20
Lean fish + lean fish products (by 10 g/d)					
Observed	0.98 (0.93, 1.04)	0.98 (0.93, 1.04)	1.07 (0.99, 1.14)	1.06 (0.99, 1.14)	
Calibrated	0.96 (0.84, 1.10)	0.96 (0.84, 1.09)	1.09 (0.96, 1.24)	1.09 (0.96, 1.24)	0.15
Fatty fish + fatty fish products (by 10 g/d)					
Observed	0.97 (0.89, 1.05)	0.97 (0.89, 1.06)	1.02 (0.94, 1.11)	1.02 (0.94, 1.12)	
Calibrated	0.99 (0.84, 1.17)	1.00 (0.85, 1.17)	1.03 (0.85, 1.23)	1.02 (0.85, 1.23)	0.85
Shellfish (by 1 g/d)					
Observed	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	
Calibrated	1.01 (0.97, 1.06)	1.01 (0.97, 1.06)	0.98 (0.95, 1.00)	0.98 (0.96, 1.00)	0.16

[1] Model 1 was stratified by center and age at baseline (1-y interval). Model 2 was additionally adjusted for BMI, smoking status, educational level, physical activity, and total energy and alcohol intakes and, in women, also adjusted for menopausal status and type, oral contraceptive use, and infertility problems. EPIC, European Prospective Investigation into Cancer and Nutrition; TC, thyroid cancer.

[2] EPIC countries with TC incidence rates >5/100,000 in women (i.e., France, Germany, Greece, Italy, and Spain).

follow-up did not alter our present findings. The most important limitations of our study include the impossibility of measuring iodine intake through questionnaires or blood samples and of distinguishing freshwater from saltwater fish (which represents the most frequently consumed type of fish in Europe). Although recall bias is unlikely to be important, an influence of dietary measurement error in the null association with fish intake cannot be ruled out, particularly considering the long duration between dietary data collection and outcome. We attempted to account for this by reanalyzing the association with calibrated fish and shellfish intakes assessed by 24-h recall with the use of an established method (31), but the results were largely unchanged.

In conclusion, the EPIC study did not show any significant association between the intake of fish and shellfish and differentiated TC risk in Europe, where very low or very high iodine intakes are rare. Further studies are needed to assess other dietary factors that could lower the risk of differentiated TC, such as fruit and vegetables, other sources of PUFAs (e.g., nuts and vegetable oils), and bioactive compounds (e.g., antioxidant vitamins, polyphenols).

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