IJC
International Journal of Cancer

Polyphenol intake and differentiated thyroid cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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

Key words: polyphenols, flavonoids, intake, thyroid cancer, cohort, EPIC

Abbreviations: BMI: body mass index; TC: thyroid cancer; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio

Conflict of interest: The authors are not aware of any conflicts of interest.

Grant sponsor: Institute of Health Carlos III and European Social Fund (ESF); **Grant sponsor:** Medical Research Council; **Grant sponsor:** Cancer Research UK; **Grant sponsor:** Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); **Grant sponsor:** The Health Research Funds; **Grant sponsor:** AGAUR - Generalitat de Catalunya; **Grant sponsor:** Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra; **Grant sponsor:** EPIC-Murcia; **Grant sponsor:** Health Research Fund (FIS); **Grant sponsor:** European Research Council; **Grant sponsor:** Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); **Grant sponsor:** Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); **Grant sponsor:** the Hellenic Health Foundation (Greece); **Grant sponsor:** German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); **Grant sponsor:** 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); **Grant sponsor:** Danish Cancer Society (Denmark); **Grant sponsor:** International Agency for Research on Cancer; **Grant sponsor:** European Commission (DG-SANCO); **Grant sponsor:** European Regional Development Fund (ERDF) "A way to build Europe."; **Grant sponsor:** Institute of Health Carlos III, Spain

DOI: 10.1002/ijc.32589

History: Received 4 Mar 2019; Accepted 18 Jun 2019; Online 25 Jul 2019

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Polyphenols are bioactive compounds with several anticarcinogenic activities; however, human data regarding associations with thyroid cancer (TC) is still negligible. Our aim was to evaluate the association between intakes of total, classes and subclasses of polyphenols and risk of differentiated TC and its main subtypes, papillary and follicular, in a European population. The European Prospective Investigation into Cancer and Nutrition cohort included 476,108 men and women from 10 European countries. During a mean follow-up of 14 years, there were 748 incident differentiated TC cases, including 601 papillary and 109 follicular tumors. Polyphenol intake was estimated at baseline using validated center/country-specific dietary questionnaires and the Phenol-Explorer database. In multivariable-adjusted Cox regression models, no association between total polyphenol and the risks of overall differentiated TC ($HR_{Q4\ vs.\ Q1}$ = 0.99, 95% confidence interval [CI] 0.77–1.29), papillary ($HR_{Q4\ vs.\ Q1}$ = 1.06, 95% CI 0.80–1.41) or follicular TC ($HR_{Q4\ vs.\ Q1}$ = 1.10, 95% CI 0.55–2.22) were found. No associations were observed either for flavonoids, phenolic acids or the rest of classes and subclasses of polyphenols. After stratification by body mass index (BMI), an inverse association between the intake of polyphenols (*p*-trend = 0.019) and phenolic acids (*p*-trend = 0.007) and differentiated TC risk in subjects with BMI ≥ 25 was observed. In conclusion, our study showed no associations between dietary polyphenol intake and differentiated TC risk; although further studies are warranted to investigate the potential protective associations in overweight and obese individuals.

What's new?

Polyphenols are secondary plant metabolites with health protective properties but whether a diet rich in polyphenols protects from thyroid cancer has not been conclusively explored. In this large prospective study, no associations were observed between dietary polyphenol intake and differentiated thyroid cancer risk. The authors recommend further studies to investigate potential associations specifically in overweight and obese individuals.

Introduction

Polyphenols (*syn*. phenolic compounds) are phytochemicals with at least one phenolic group in their structure. Polyphenols are chemically classified as flavonoids, phenolic acids, stilbenes and lignans. To date, several thousands of polyphenols have been described, some of which are widely spread in the plant kingdom, while some of them are very specific to one plant species/genus.[1] Polyphenols are plant secondary metabolites that are involved in defense strategies, protecting plants against pathogens, ultraviolet radiation and oxidation. In humans, polyphenols may reduce the risk of chronic diseases, such as cardiovascular diseases, type 2 diabetes and several types of cancer.[1–4]

Thyroid cancer (TC) is the most common endocrine cancer, and it is the seventh most frequent cancer in European women.[5] TC incidence has been steadily increasing in the last decades in many countries worldwide. This is partially due to the routine use of more sensitive diagnostic techniques (ultrasonography, computed tomography and magnetic resonance imaging), combined with increased medical surveillance; although changes in environmental factors likely also play a role.[6] However, only few risk factors (benign thyroid disease, radiation exposure, body size) are known for this disease.[6–8] While dietary factors are not consistently associated with TC so far,[9] a 2014 US-based cohort have shown that two flavonoid subclasses, flavan-3-ols and flavanones, were related to TC risk, in opposite directions.[10] No studies have investigated the association with other classes of polyphenols. Therefore, our aim was to evaluate the relationships between the intake of all classes (flavonoids, phenolic acids, lignans and stilbenes) and 22 subclasses of polyphenols and the risk of differentiated TC, and their histological subtypes (papillary and follicular TC) in a large prospective European study, with a high heterogeneity in polyphenol intake[11] and in TC incidence among countries.

Materials and Methods

Subjects and study design

The current study used data from the European Prospective Investigation into Cancer and Nutrition (EPIC), an ongoing multicenter prospective cohort including over half a million subjects from 10 European countries.[12] Most of the participants were enrolled between 1992 and 1998 at ages between 35 and 70 years from the general population, with some exceptions described previously.[12] All participants gave written informed consent, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer. Participants were excluded from the analyses if they had a previous cancer other than nonmelanoma skin cancer at baseline or had missing information on date of diagnosis or incomplete follow-up data (n = 29,332), had missing data on lifestyle factors (n = 1,277), had missing dietary data or extreme energy intake and/or expenditure (participant in the top or the bottom 1% of the distribution of the ratio of total energy intake to energy requirement; n = 14,555) (Supplementary Fig. S1).

Identification and follow-up of TC cases

Incident cancer cases were identified through record linkage with population cancer registries in most countries. In France, Germany and Greece, a combination of methods was used including health insurance records, cancer and pathology registries and by active follow-up of study participants and their next of kin. Vital status was collected from regional or national mortality registries. Complete follow-up censoring dates varied among centers, ranging between December 2010 and December 2014. A total of 857 cases were defined as participants with a first primary TC (code C73 according to the International Classification of Diseases, 10th Revision) during the follow-up, of whom 57 were excluded due to the exclusion criteria mentioned in the "Subjects and study design" section. Poorly differentiated TC (e.g., anaplastic [n = 9], medullary [n = 37], lymphoma [n = 1] or "other morphologies" [n = 5]) were also excluded (Fig. S1). Thus, we only included differentiated TC, that is, papillary (n = 601), follicular (n = 109) and not otherwise specified TC (n = 38) which are also likely to be papillary tumors. Data on the stage of differentiated TC at diagnosis were collected from each center, where possible. A total of 468 cases (63%) had stage information, of which 371 were classified as low-risk (tumor-node-metastasis staging score of T1–T2) and 97 were classified as high-risk tumors (T3–T4).

Dietary assessment and data collection

Habitual diet of the preceding year was collected using a validated country/center-specific dietary questionnaire at baseline.[12,13] Most centers utilized a self-administered food frequency questionnaire. In the remaining centers (Greece, Spain and Ragusa and Naples [Italy]), a face-to-face dietary questionnaire was employed to collect dietary information. In Malmö (Sweden), a method combining a short nonquantitative food frequency questionnaire with a 7-day dietary diary was used. Total energy and nutrient intakes were estimated by using the standardized EPIC Nutrient Database.[14] Polyphenol intake was estimated using the Phenol-Explorer database,[15] including retention factors for cooked and processed foods,[16] as previously described.[11,17]

Lifestyle questionnaires were used to collect data on lifetime and current smoking status, physical activity, education, menstrual and reproductive history. Height and weight were measured at the baseline in most centers. In EPIC-Oxford, Norway and France, anthropometric measurements were self-reported.[12]

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between total, 4 classes and 22 subclasses (Table 2) of polyphenol intakes and TC risk were estimated using multivariable Cox proportional hazard models with age as the time scale. The proportional hazards assumption was evaluated in all models by using an analysis of Schoenfeld residuals, and no evidence of violation was detected. Polyphenol intake was analyzed as sex-specific quartiles using both absolute intakes (mg/d) and intakes

adjusted for energy as density variables (mg/2,000 kcal*d), with similar results. Tests for trend were performed by assigning a score between 1 and 4 according to their sex-specific quartile and entered this variable as a continuous term in the Cox regression models. Polyphenol intakes were also analyzed as continuous variables, after $\log_2$ transformation to improve normality of intake distributions. Model 1 was stratified by EPIC study center, sex and age at recruitment (1-year interval). Model 2 was additionally adjusted for potential confounders, that is, variables associated with TC risk in previous EPIC works[18–21]: body mass index (BMI), smoking status (never, former, current and not specified), educational level (primary or lower; secondary or higher, and not specified), physical activity classified according to the Cambridge Physical Activity Index (inactive, active and not specified)[22] and total energy and alcohol intakes. In women, Model 2 was also adjusted for menopausal status and type (premenopausal, perimenopausal, postmenopausal, surgical menopause), ever use of oral contraceptive and infertility problems. Results from both models were almost identical, and therefore, the most adjusted model was chosen for presentation. In order to evaluate the impact of fruit and vegetable consumption in our results, we further adjusted Model 2 for fiber (as a proxy of their intake).

Possible interactions, on the multiplicative scale, with sex, smoking status (never, former or current smokers), alcohol intake (for women <15 *vs.* ≥15 g/d; and for men <30 *vs.* ≥30 g/d) and BMI (<25 *vs.* ≥25 kg/m^2) were examined by including the interaction terms in the most-adjusted models. The statistical significance of the cross-product terms were evaluated using the likelihood ratio test. If there was evidence of a potential multiplicative interaction (p for interaction <0.1), the interactions on the additive scale were computed using the relative excess risks due to interaction.[23]

Separate models were defined to assess the risk of TC by subtype (papillary and follicular). The Wald test was used to evaluate the heterogeneity of risk between TC subtypes. Similar models were also computed to check the variability between countries with a high compared to low TC incidence. EPIC countries with TC incidence rates per year of >1/10,000 in women (i.e., France, Germany, Greece, Italy and Spain) were considered to have high TC incidence. Moreover, separate models were conducted only in women, because most of the cases occurred in females (89%). Separate models were also performed to evaluate the heterogeneity between low risk (T1–T2) and high risk tumor (T3–T4) cases, as a way to control for potential overdiagnosis. We also conducted two sensitivity models, excluding 77 cases that were diagnosed with TC within the first 2 years of follow-up, because some participants may have modified their diet during the prediagnostic period of the disease. All p values presented are two-tailed and were considered to be statistically significant when $p < 0.05$. To account for multiple testing for the subclasses of polyphenols, Bonferroni correction was used and then results were considered statistically significant if $p < 0.05/26$ (number of tests for the intakes of all polyphenol classes and subclasses) = 0.002. All statistical analyses were conducted by using R 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Data availability

For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Results

The final analytical cohort included 476,108 men and women. During 13.9 (4.0) years of mean (SD) follow-up, 748 (89.0% women) incident first differentiated TC cases were identified, including 601 papillary and 109 follicular tumors. The highest median of total polyphenol intakes was in Denmark (1,573 mg/d); whereas the lowest intake was 653 mg/d in Norway (data not tabulated). Participants with the highest polyphenol intake were older and more physically active, had a higher educational level and lower BMI, included a higher proportion of current smokers, and consumed less alcohol and total energy at recruitment, compared to those with the lowest intake (Table 1). Women in the highest quartile of polyphenol intake tended to be postmenopausal or to have undergone surgical menopause, to have more infertility problems, and to take more oral contraceptives at the baseline.

In basic (Table S1) and multivariable models (Table 2), total polyphenol intake was not associated with the risk of differentiated TC using either absolute amounts ($HR_{Q4\ vs.\ Q1}$ = 0.99, 95% CI 0.77–1.29; p-trend = 0.97) (Table 2) or nutrient density ($HR_{Q4\ vs.\ Q1}$ = 1.01, 95% CI 0.79–1.29; p-trend = 0.71) (Table S2). No associations were observed in any cancer subtype: papillary ($HR_{Q4\ vs.\ Q1}$ = 1.06, 95% CI 0.80–1.41; p-trend = 0.55) and follicular tumors ($HR_{Q4\ vs.\ Q1}$ = 1.10, 95% CI 0.55–2.22; p-trend = 0.93) (Table 3). Null results were also observed for all classes and subclasses of polyphenols with the risk of overall differentiated TC and papillary TC. For follicular TC, an inverse association was found with the intake of quartiles of theaflavins and anthocyanidins; while a direct association was detected with the consumption of quartiles of hydroxyinnamic acids, alkylmethoxyphenols and methoxyphenols; but not using the continuous variables (after $\log_2$ transformation). Furthermore, none of these associations reached the Bonferroni corrected significance level (p = 0.002). Finally, results of Model 2 additionally adjusted for fiber were similar to those without the adjustment (data not shown).

In separate models, no associations between total polyphenol intake and differentiated TC were found in women ($HR_{Q4\ vs.\ Q1}$ = 1.00, 95% CI 0.77–1.32; p-trend = 0.91); in either high ($HR_{Q4\ vs.\ Q1}$ = 0.98, 95% CI 0.74–1.29; p-trend = 0.87) or low TC incidence rate EPIC countries ($HR_{Q4\ vs.\ Q1}$ = 0.99, 95% CI 0.55–1.77; p-trend = 0.95); and in either low risk ($HR_{Q4\ vs.\ Q1}$ = 1.00, 95% CI 0.70–1.43; p-trend = 0.96) or high risk tumors ($HR_{Q4\ vs.\ Q1}$ = 1.23, 95% CI 0.60–2.51; p-trend = 0.22) (Table S2). In the sensitivity analysis, excluding TC cases diagnosed in the first 2 years of follow-up ($HR_{Q4\ vs.\ Q1}$ = 0.97, 95% CI 0.74–1.27; p-trend = 0.84) (Table S2), the results were practically identical to results based on the whole cohort.

No statistically significant multiplicative interactions between total polyphenol intake and differentiated TC risk on the multivariable models with sex, BMI, smoking status and baseline

Table 1. Baseline characteristics of the participants according to sex-specific quartiles of total polyphenol intake in the EPIC study

Baseline characteristics	All	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Polyphenol (mg/d), men		50–837	838–1,149	1,150–1,539	1,540–9,521
Polyphenol (mg/d), women		14–738	739–1,053	1,054–1,460	1,460–10,615
Country, %					
France	14.2	6.9	10.7	16.1	22.9
Italy	9.4	12.4	14.1	8.7	2.2
Spain	8.4	18.5	8.6	4.5	2.0
United Kingdom	15.8	4.5	8.3	20.1	30.4
The Netherlands	7.7	3.5	8.9	12.8	5.5
Greece	5.5	9.4	6.6	3.9	2.0
Germany	10.2	8.4	13.5	11.9	7.0
Sweden	10.2	16.1	15.2	7.4	2.2
Denmark	11.6	2.2	5.5	12.8	25.7
Norway	7.1	18.1	8.5	1.8	0.1
Sex, women, %	70.1	70.1	70.1	70.1	70.1
Age (year), mean (SD)	51.2 (9.9)	50.8 (9.9)	50.6 (9.9)	51.4 (10.1)	52.1 (9.7)
BMI (kg/m^2), mean (SD)	25.4 (4.3)	26.0 (4.5)	25.5 (4.3)	25.2 (4.2)	25.0 (4.1)
Alcohol (g/d), median (p25–p75)	5.3 (0.9–14.9)	2.1 (0.1–8.5)	4.8 (0.9–13.5)	7.1 (1.6–17.9)	8.8 (2.1–20.6)
Total energy (kcal/d), mean (SD)	2,075 (619)	1,811 (543)	2,022 (571)	2,145 (602)	2,321 (640)
Smoking status, %					
Never	49.0	53.6	48.8	48.1	45.3
Former	26.6	23.6	26.1	27.7	29.0
Current	22.4	20.6	23.3	22.3	23.3
Education level, secondary, %	66.5	56.4	65.0	70.9	73.5
Physical activity, active, %	44.2	40.2	43.1	45.5	48.2
Prevalence diabetes, yes, %	2.6	3.7	2.6	2.2	2.0
Menopausal status[1], %					
Premenopausal	34.8	36.5	36.9	34.0	31.8
Postmenopausal	43.2	40.9	41.0	44.8	46.0
Perimenopausal	19.1	19.8	19.5	18.1	19.1
Surgical menopause	2.9	2.8	2.7	3.0	3.1
Ever use of oral contraceptive use[1], yes, %	57.2	48.9	55.3	61.0	63.5
Infertility problems[1], yes, %	3.1	2.5	2.7	3.3	3.9

Missing values (classified as not specified): smoke status (n = 9,676; 2.0%), education level (n = 16,929; 3.6%), physical activity (n = 8,824; 1.9%), diabetes (38,970; 8.2%), ever use of oral contraceptive (n = 8,427; 2.5%), infertility problems (n = 111,162; 33.3%).
[1]Only in women (n = 333,876; 70.1%).
Abbreviation: p25 and p75, percentile 25th and 75th.

alcohol intake were detected. A weak effect modification (p for interaction = 0.11) by BMI for the association of phenolic acid intake and differentiated TC risk was found. Associations between polyphenol intake and differentiated TC risk in subjects with a BMI less than and ≥25 is shown in Table 4. An inverse association between the intake of both total polyphenols and phenolic acids and differentiated TC, particularly papillary TC, in subjects with a BMI ≥ 25; but not in those with BMI < 25 (p for interaction = 0.28). However, they did not reach the Bonferroni threshold (Table 3). Similarly, a borderline statistically significant interaction, on the additive scale, was observed by BMI for total polyphenol (p for interaction = 0.08) and for phenolic acids (p for interaction = 0.06) (Fig. S2).

Discussion

To our knowledge, this is the first study extensively evaluating the associations of the intake of all polyphenols and differentiated TC risk, and showed no associations between the intake of total, classes and subclasses of polyphenols with risk of differentiated TC and its subtypes (papillary and follicular tumors). It is a large prospective study (n = 476,108), with a long follow-up (mean = 14 years), and a relatively high number of cases (n = 748). Moreover, it covers 10 European countries with a large heterogeneity in polyphenol intakes and differentiated TC incidence.[11] Polyphenol intake was higher in non-Mediterranean EPIC countries compared to Mediterranean EPIC countries. In non-Mediterranean countries, coffee and tea accounted for ~60% of total polyphenols, while in

Table 2. Hazard ratios (95% CIs) for thyroid cancer, according to the intake of sex-specific quartiles of polyphenol classes and subclasses in the EPIC study

		Overall TC risk					
Polyphenol classes and subclasses	**Intake (mg/d) Median (P25–P75)**	**Quartile 1 HR (95% CI)**	**Quartile 2 HR (95% CI)**	**Quartile 3 HR (95% CI)**	**Quartile 4 HR (95% CI)**	***p*-trend**	**Continuous (log2)**
Polyphenols	1,083.3 (767.1–1,485.0)	1 (ref)	0.86 (0.70–1.06)	0.90 (0.72–1.14)	0.99 (0.77–1.29)	0.97	0.97 (0.86–1.11)
Flavonoids	419.5 (254.4–689.6)	1 (ref)	1.10 (0.89–1.37)	1.21 (0.96–1.53)	1.10 (0.84–1.45)	0.35	1.06 (0.96–1.16)
Flavanols	284.8 (157.8–516.9)	1 (ref)	1.03 (0.83–1.29)	1.35 (1.07–1.70)**	1.00 (0.76–1.33)	0.34	1.02 (0.94–1.10)
Flavan-3-ols	40.7 (17.7–148.7)	1 (ref)	1.22 (0.98–1.52)	1.33 (1.04–1.70)**	1.11 (0.84–1.48)	0.33	1.01 (0.96–1.06)
Proanthocyanidins	203.1 (123.9–311.8)	1 (ref)	1.04 (0.84–1.30)	1.10 (0.87–1.38)	1.18 (0.91–1.52)	0.20	1.04 (0.95–1.13)
Theaflavins[1]	1.5 (0.0–29.6)	1 (ref)	1.11 (0.90–1.38)	1.25 (1.01–1.55)*	0.82 (0.60–1.11)	0.88	1.00 (1.00–1.01)
Flavonols	28.4 (16.1–53.2)	1 (ref)	1.10 (0.89–1.37)	1.18 (0.93–1.49)	1.00 (0.76–1.33)	0.78	1.00 (0.92–1.09)
Flavanones	25.3 (10.3–55.4)	1 (ref)	1.09 (0.89–1.34)	1.23 (1.00–1.52)*	1.21 (0.97–1.51)	0.05	1.05 (1.01–1.09)*
Anthocyanins	24.6 (12.4–51.7)	1 (ref)	1.04 (0.82–1.32)	1.01 (0.79–1.29)	1.16 (0.89–1.52)	0.31	0.99 (0.94–1.04)
Flavones	9.3 (5.8–14.8)	1 (ref)	1.09 (0.87–1.38)	1.10 (0.86–1.39)	1.22 (0.94–1.58)	0.16	1.07 (0.98–1.18)
Dihydrochalcones	1.7 (0.7–3.1)	1 (ref)	1.07 (0.87–1.31)	1.17 (0.95–1.44)	1.01 (0.80–1.29)	0.61	1.00 (0.98–1.02)
Dihydroflavonols	0.5 (0.0–2.8)	1 (ref)	0.94 (0.75–1.18)	0.98 (0.79–1.22)	1.01 (0.78–1.31)	0.94	1.00 (0.99–1.01)
Isoflavonoids	0.0 (0.0–0.1)	1 (ref)	0.98 (0.80–1.21)	0.97 (0.78–1.21)	0.96 (0.74–1.26)	0.78	0.98 (0.97–1.00)
Phenolic acids	522.0 (324.6–757.3)	1 (ref)	0.78 (0.63–0.96)*	0.72 (0.58–0.90)**	0.98 (0.79–1.21)	0.65	0.95 (0.87–1.02)
Hydroxycinnamic	487.0 (274.8–717.3)	1 (ref)	0.81 (0.66–1.00)*	0.75 (0.60–0.94)**	1.02 (0.83–1.27)	0.98	0.96 (0.90–1.03)
Hydroxybenzoics	20.7 (7.1–58.9)	1 (ref)	1.16 (0.92–1.47)	1.35 (1.03–1.77)*	1.13 (0.83–1.55)	0.36	1.02 (0.97–1.08)
Hydroxyphenylacetic	0.1 (0.0–0.3)	1 (ref)	0.98 (0.80–1.21)	0.89 (0.71–1.11)	0.87 (0.67–1.14)	0.24	0.98 (0.95–1.01)
Stilbenes	0.5 (0.1–2.0)	1 (ref)	1.31 (1.05–1.63)*	1.22 (0.96–1.53)	1.20 (0.91–1.58)	0.23	1.02 (0.98–1.06)
Lignans	1.5 (1.1–2.1)	1 (ref)	0.95 (0.76–1.20)	1.03 (0.82–1.31)	0.84 (0.64–1.11)	0.37	0.95 (0.85–1.07)
Other polyphenols							
Alkylphenols	27.6 (10.9–48.4)	1 (ref)	1.03 (0.84–1.27)	1.10 (0.86–1.40)	0.82 (0.61–1.11)	0.47	0.96 (0.91–1.01)
Tyrosols	3.8 (1.4–10.9)	1 (ref)	1.22 (0.95–1.55)	1.20 (0.92–1.56)	1.02 (0.74–1.41)	0.84	0.97 (0.92–1.01)
Alkylmethoxyphenols	2.4 (1.2–3.7)	1 (ref)	0.80 (0.65–0.98)*	0.77 (0.61–0.96)*	1.08 (0.88–1.34)	0.63	0.99 (0.96–1.02)
Methoxyphenols	0.3 (0.1–0.4)	1 (ref)	0.78 (0.63–0.95)*	0.70 (0.56–0.88)**	1.05 (0.85–1.29)	0.95	0.99 (0.98–1.00)
Hydroxybenzaldehydes	0.1 (0.0–0.5)	1 (ref)	0.89 (0.71–1.13)	0.94 (0.75–1.20)	1.13 (0.86–1.50)	0.46	0.98 (0.95–1.01)
Hydroxyphenylpropenes[1]	0.0 (0.0–0.6)	1 (ref)	1.18 (0.91–1.52)	0.95 (0.73–1.24)	0.98 (0.67–1.44)	0.59	1.00 (0.99–1.01)
Hydroxycoumarins	0.0 (0.0–0.2)	1 (ref)	1.05 (0.85–1.30)	1.08 (0.85–1.36)	0.92 (0.68–1.26)	0.91	1.01 (0.99–1.03)
Furanocoumarins	0.0 (0.0–0.1)	1 (ref)	1.09 (0.86–1.38)	1.28 (1.01–1.63)*	0.86 (0.66–1.12)	0.54	1.00 (0.98–1.01)

Cox model was stratified by sex, age and center, and additionally adjusted for smoking status, education level, body mass index (kg/m^2), physical activity, total energy intake (kcal/d) and alcohol (g/d) intakes and in women also for menopausal status, oral contraceptive use and infertility problems.
[1]Classified as nonconsumers and tertiles of consumers.
*$p < 0.05$; **$p < 0.01$; no associations exceed the Bonferroni threshold ($p < 0.05/26$) = 0.002.

Mediterranean countries coffee (36%), fruits (25%) and wine (10%) were the main food sources.[11]

Our study has some limitations. First, although we have used center/country-specific validated dietary questionnaires[13] and Phenol-Explorer, which is the most comprehensive food composition database on polyphenols to date,[15] measurement error in collecting and estimating dietary polyphenol intake remains an issue and may have led to an underestimation of any true association. Second, dietary and lifestyle data were only evaluated at baseline, and, therefore, changes in these variables during the 14 years of mean follow-up are not accounted for. Another limitation is the potential impact of the large variations of polyphenol intake between EPIC countries that have led to their unequal representation in the extreme intake quartiles. The impact of overdiagnosis in our study may also be a limitation; however, the results were similar in the countries with high or low incidence rates and in the associations with low- or high-risk TC at the diagnosis. Finally, an influence of dietary changes during the prediagnostic period of the TC is unlikely as sensitivity analyses excluding incident cases diagnosed in the first 2 year of follow-up provide reassurance against this possibility.

Null results were also observed not only with overall intake of polyphenols but also with the intake of total flavonoids and flavonoid subclasses. In contrast, the NIH-AARP Diet and Health Study, a comparable size cohort in the United States, observed a significantly inverse relationship of flavan-3-ol monomers with TC risk.[10] In our study, we did not find any association with flavan-3-ol monomers. This null finding is in line with the lack of associations in EPIC between TC risk and intakes of any fruit group[24] or tea,[25] which are the main food sources of flavan-3-ol

Table 3. Hazard ratios (95% CIs) of the associations between polyphenol classes and the risk of papillary and follicular thyroid cancers in the EPIC study

	Papillary TC risk						Follicular TC risk						
Polyphenol classes and subclasses	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	*p*-trend	Continuous (log2)	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	*p*-trend	Continuous (log2)	*p* for heterogeneity[2]
Polyphenols	1 (ref)	0.86 (0.68–1.09)	0.97 (0.74–1.25)	1.06 (0.80–1.41)	0.55	0.99 (0.86–1.14)	1 (ref)	1.05 (0.60–1.81)	0.89 (0.47–1.66)	1.10 (0.55–2.22)	0.93	1.02 (0.72–1.45)	0.58
Flavonoids	1 (ref)	1.11 (0.87–1.43)	1.34 (1.03–1.75)*	1.21 (0.89–1.64)	0.11	1.10 (0.98–1.22)	1 (ref)	0.94 (0.56–1.60)	0.77 (0.42–1.38)	0.76 (0.38–1.52)	0.33	0.88 (0.70–1.12)	0.12
Flavanols	1 (ref)	1.08 (0.85–1.39)	1.48 (1.14–1.93)**	1.11 (0.81–1.51)	0.13	1.05 (0.96–1.15)	1 (ref)	0.77 (0.45–1.31)	0.82 (0.46–1.45)	0.57 (0.28–1.18)	0.20	0.89 (0.78–1.02)	0.08
Flavan-3-ols	1 (ref)	1.23 (0.96–1.58)	1.42 (1.08–1.87)**	1.23 (0.90–1.68)	0.12	1.04 (0.99–1.10)	1 (ref)	0.95 (0.55–1.61)	0.74 (0.40–1.35)	0.58 (0.28–1.19)	0.10	0.88 (0.79–0.98)*	0.033
Proanthocyanidins	1 (ref)	1.02 (0.80–1.31)	1.17 (0.90–1.51)	1.18 (0.88–1.57)	0.17	1.06 (0.96–1.17)	1 (ref)	1.13 (0.66–1.92)	0.58 (0.30–1.13)	1.27 (0.67–2.42)	0.91	0.94 (0.79–1.10)	0.66
Theaflavins[1]	1 (ref)	1.12 (0.88–1.43)	1.36 (1.08–1.72)**	0.90 (0.64–1.26)	0.36	1.01 (1.00–1.01)	1 (ref)	0.82 (0.48–1.40)	0.63 (0.35–1.13)	0.42 (0.18–0.95)*	0.023	0.98 (0.97–1.00)	0.014
Flavonols	1 (ref)	1.02 (0.80–1.31)	1.16 (0.89–1.51)	1.02 (0.74–1.39)	0.65	1.03 (0.93–1.13)	1 (ref)	1.01 (0.59–1.72)	1.17 (0.66–2.10)	0.74 (0.35–1.56)	0.70	0.90 (0.76–1.07)	0.59
Flavanones	1 (ref)	1.13 (0.90–1.42)	1.23 (0.97–1.55)	1.17 (0.92–1.50)	0.15	1.04 (0.99–1.09)	1 (ref)	0.99 (0.57–1.72)	1.24 (0.71–2.15)	1.44 (0.82–2.53)	0.15	1.13 (1.01–1.26)*	0.45
Anthocyanins	1 (ref)	1.12 (0.85–1.47)	1.07 (0.81–1.42)	1.37 (1.01–1.85)*	0.06	1.00 (0.95–1.06)	1 (ref)	0.58 (0.33–1.02)	0.72 (0.42–1.25)	0.47 (0.24–0.91)*	0.05	0.95 (0.87–1.04)	0.010
Flavones	1 (ref)	1.10 (0.85–1.44)	1.09 (0.83–1.43)	1.32 (0.99–1.77)	0.07	1.11 (1.00–1.24)	1 (ref)	0.91 (0.53–1.57)	0.84 (0.47–1.49)	0.55 (0.28–1.11)	0.11	0.93 (0.73–1.17)	0.028
Dihydrochalcones	1 (ref)	0.99 (0.79–1.24)	1.11 (0.88–1.40)	1.05 (0.81–1.37)	0.48	0.99 (0.97–1.02)	1 (ref)	1.52 (0.86–2.68)	1.80 (1.03–3.16)*	0.83 (0.42–1.62)	0.86	1.00 (0.95–1.06)	0.65
Dihydroflavonols	1 (ref)	0.94 (0.73–1.21)	0.96 (0.75–1.22)	0.98 (0.73–1.32)	0.86	0.99 (0.98–1.01)	1 (ref)	0.93 (0.53–1.63)	0.95 (0.53–1.69)	0.83 (0.39–1.76)	0.69	1.01 (0.98–1.05)	0.62
Isoflavonoids	1 (ref)	0.89 (0.71–1.13)	0.91 (0.71–1.15)	0.98 (0.73–1.32)	0.78	0.98 (0.97–1.00)	1 (ref)	1.89 (1.08–3.30)*	1.68 (0.90–3.14)	0.92 (0.42–2.01)	0.98	0.98 (0.94–1.03)	0.93
Phenolic acids	1 (ref)	0.72 (0.57–0.91)**	0.69 (0.54–0.89)**	0.91 (0.72–1.15)	0.36	0.93 (0.85–1.01)	1 (ref)	1.20 (0.67–2.14)	1.08 (0.59–2.01)	1.85 (1.00–3.43)*	0.09	1.14 (0.91–1.43)	0.05
Hydroxycinnamic	1 (ref)	0.74 (0.59–0.93)**	0.65 (0.50–0.84)**	0.96 (0.76–1.20)	0.51	0.94 (0.87–1.02)	1 (ref)	1.59 (0.86–2.93)	1.59 (0.85–2.99)	2.33 (1.23–4.44)**	0.015	1.17 (0.95–1.44)	0.012
Hydroxybenzoics	1 (ref)	1.17 (0.89–1.54)	1.47 (1.08–2.01)**	1.29 (0.91–1.84)	0.10	1.05 (0.99–1.12)	1 (ref)	1.03 (0.59–1.80)	0.78 (0.40–1.52)	0.54 (0.25–1.20)	0.10	0.88 (0.77–1.01)	0.030
Hydroxyphenylacetic	1 (ref)	0.99 (0.78–1.25)	0.87 (0.68–1.11)	0.79 (0.59–1.07)	0.10	0.97 (0.94–1.00)	1 (ref)	0.79 (0.47–1.32)	0.90 (0.51–1.59)	1.00 (0.47–2.16)	0.87	1.03 (0.95–1.13)	0.52
Stilbenes	1 (ref)	1.43 (1.11–1.83)**	1.28 (0.98–1.66)	1.22 (0.89–1.67)	0.27	1.02 (0.98–1.07)	1 (ref)	0.83 (0.48–1.45)	0.92 (0.52–1.65)	0.78 (0.37–1.66)	0.61	1.01 (0.92–1.11)	0.34
Lignans	1 (ref)	1.01 (0.79–1.30)	1.02 (0.79–1.34)	0.85 (0.63–1.16)	0.35	0.96 (0.85–1.09)	1 (ref)	0.68 (0.38–1.22)	0.96 (0.53–1.74)	0.91 (0.45–1.84)	0.95	1.03 (0.77–1.38)	0.76
Other polyphenols													
Alkylphenols	1 (ref)	1.06 (0.84–1.32)	1.11 (0.85–1.45)	0.69 (0.49–0.99)*	0.23	0.95 (0.90–1.01)	1 (ref)	0.87 (0.46–1.63)	1.13 (0.57–2.22)	1.29 (0.61–2.71)	0.42	1.04 (0.89–1.21)	0.22
Tyrosols	1 (ref)	1.32 (1.00–1.75)*	1.31 (0.97–1.77)	1.13 (0.79–1.63)	0.52	0.96 (0.91–1.01)	1 (ref)	0.86 (0.50–1.47)	0.60 (0.31–1.16)	0.54 (0.23–1.28)	0.13	0.98 (0.87–1.10)	0.09
Alkylmethoxyphenols	1 (ref)	0.81 (0.64–1.01)	0.71 (0.55–0.92)**	1.03 (0.82–1.30)	0.90	0.98 (0.95–1.01)	1 (ref)	0.82 (0.45–1.47)	1.08 (0.60–1.95)	1.81 (1.01–3.25)*	0.034	1.07 (0.96–1.18)	0.043
Methoxyphenols	1 (ref)	0.71 (0.56–0.89)*	0.60 (0.46–0.77)**	0.99 (0.79–1.24)	0.58	0.99 (0.97–1.00)	1 (ref)	1.33 (0.73–2.41)	1.53 (0.84 2.79)	2.00 (1.07–3.71)*	0.027	1.03 (0.98–1.08)	0.023
Hydroxybenzaldehydes	1 (ref)	0.88 (0.68–1.14)	0.90 (0.69–1.18)	1.05 (0.76–1.44)	0.88	0.98 (0.94–1.02)	1 (ref)	0.90 (0.49–1.64)	1.05 (0.56–1.95)	1.21 (0.56–2.58)	0.61	1.02 (0.93–1.11)	0.58
Hydroxyphenylpropenes[1]	1 (ref)	1.24 (0.94–1.63)	0.97 (0.72–1.29)	1.07 (0.68–1.67)	0.76	1.00 (0.99–1.02)	1 (ref)	1.01 (0.43–2.37)	1.10 (0.49–2.46)	1.09 (0.42–2.81)	0.83	1.00 (0.97–1.04)	0.66
Hydroxycoumarins	1 (ref)	1.03 (0.82–1.30)	0.98 (0.75–1.27)	0.84 (0.58–1.20)	0.43	1.00 (0.98–1.02)	1 (ref)	0.96 (0.54–1.69)	1.08 (0.57–2.02)	1.20 (0.55–2.63)	0.62	1.05 (0.99–1.11)	0.38
Furanocoumarins	1 (ref)	1.05 (0.80–1.36)	1.26 (0.97–1.63)	0.81 (0.61–1.09)	0.39	1.00 (0.98–1.02)	1 (ref)	1.22 (0.66–2.24)	1.18 (0.61–2.29)	0.84 (0.38–1.84)	0.71	1.00 (0.96–1.05)	0.74

Cox model was stratified by sex, age and center, and additionally adjusted for smoking status, education level, body mass index (kg/m^2), physical activity, total energy intake (kcal/d) and alcohol (g/d) intakes and in women also for menopausal status, oral contraceptive use and infertility problems.

[1]Classified as nonconsumers and tertiles of consumers.

[2]*p*-Value for heterogeneity for papillary *versus* follicular cancer using the Wald test.

*$p < 0.05$; **$p < 0.01$; no associations exceed the Bonferroni threshold ($p < 0.05/26$) = 0.002.

Table 4. Hazard ratio for differentiated thyroid cancer (TC), stratified by BMI according to the intake of sex-specific quartiles total polyphenols, flavonoids and phenolic acids in the EPIC study

	BMI < 25							BMI ≥ 25							
	No. of cases	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	*p*-trend	Continuous (log2)	No. of cases	Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	*p*-trend	Continuous (log2)	*p*-interaction
Overall TC risk	748														
Polyphenols	396	1.00 (ref.)	0.95 (0.70–1.29)	1.05 (0.76–1.46)	1.36 (0.96–1.92)	0.05	1.13 (0.94–1.35)	352	1.00 (ref.)	0.76 (0.57–1.01)	0.73 (0.52–1.02)	0.62 (0.42–0.93)*	0.019	0.82 (0.68–0.98)*	0.30
Flavonoids	396	1.00 (ref.)	1.08 (0.78–1.49)	1.24 (0.89–1.73)	1.20 (0.83–1.74)	0.25	1.08 (0.94–1.23)	352	1.00 (ref.)	1.12 (0.84–1.51)	1.14 (0.82–1.58)	0.96 (0.63–1.46)	0.96	1.03 (0.90–1.19)	0.94
Phenolic acids	396	1.00 (ref.)	0.84 (0.62–1.13)	0.88 (0.64–1.20)	1.24 (0.92–1.65)	0.13	1.04 (0.93–1.16)	352	1.00 (ref.)	0.70 (0.53–0.94)*	0.56 (0.40–0.78)**	0.69 (0.49–0.96)*	0.007	0.85 (0.75–0.95)**	0.11
Papillary TC risk	601														
Polyphenols	326	1.00 (ref.)	0.89 (0.63–1.26)	1.09 (0.76–1.57)	1.41 (0.96–2.06)	0.04	1.12 (0.93–1.36)	275	1.00 (ref.)	0.80 (0.57–1.11)	0.78 (0.53–1.13)	0.64 (0.41–1.01)	0.06	0.83 (0.67–1.01)	0.46
Flavonoids	326	1.00 (ref.)	1.09 (0.76–1.57)	1.34 (0.92–1.94)	1.31 (0.87–1.98)	0.12	1.11 (0.96–1.28)	275	1.00 (ref.)	1.12 (0.80–1.58)	1.28 (0.88–1.85)	1.01 (0.63–1.62)	0.63	1.07 (0.91–1.25)	0.93
Phenolic acids	326	1.00 (ref.)	0.82 (0.59–1.14)	0.74 (0.52–1.05)	1.15 (0.84–1.57)	0.43	1.01 (0.90–1.14)	275	1.00 (ref.)	0.62 (0.44–0.86)**	0.60 (0.42–0.87)**	0.61 (0.42–0.90)*	0.009	0.83 (0.73–0.94)**	0.28
Follicular TC risk	109														
Polyphenols	53	1.00 (ref.)	1.16 (0.51–2.67)	0.94 (0.37–2.40)	1.36 (0.50–3.69)	0.67	1.22 (0.72–2.09)	56	1.00 (ref.)	0.95 (0.45–2.01)	0.87 (0.37–2.06)	0.96 (0.35–2.62)	0.87	0.94 (0.60–1.49)	0.85
Flavonoids	53	1.00 (ref.)	1.00 (0.44–2.25)	0.80 (0.33–1.94)	0.81 (0.30–2.19)	0.57	0.89 (0.63–1.27)	56	1.00 (ref.)	0.92 (0.45–1.87)	0.79 (0.35–1.76)	0.78 (0.28–2.15)	0.54	0.90 (0.65–1.25)	0.99
Phenolic acids	53	1.00 (ref.)	1.05 (0.41–2.64)	1.71 (0.72–4.08)	2.06 (0.82–5.17)	0.06	1.29 (0.91–1.82)	56	1.00 (ref.)	1.32 (0.62–2.79)	0.58 (0.22–1.54)	1.63 (0.69–3.86)	0.59	1.05 (0.78–1.42)	0.08

Cox model was stratified by sex, age and center, and additionally adjusted for smoking status, education level, body mass index (kg/m^2), physical activity, total energy intake (kcal/d) and alcohol (g/d) intakes and in women also for menopausal status, oral contraceptive use and infertility problems.
*$p < 0.05$; **$p < 0.01$; no associations exceed the Bonferroni threshold ($p < 0.05/26$) = 0.002.

monomers.[11] In the NIH-AARP Diet and Health Study, a significantly positive association between flavanone intake and TC risk was observed which was mainly associated with the high consumption of orange and grapefruit juices, but not to the intake of oranges and tangelos.[10] In EPIC, a positive association of fruit juice consumption and TC risk was also detected. However, this was probably due to their high content in sugar,[21] and not due to their high content in flavanones,[24] as diabetes is a probable risk factor of TC.[26]

In a case–control study conducted in the San Francisco Bay Area, isoflavone intake and its main food sources (i.e., soy-based foods and alfalfa sprouts) were inversely associated with TC risk,[27] but not in prospective studies, such as our study and the NIH-AARP Diet and Health Study.[10]

In the current study, no associations were observed with phenolic acids, lignans, stilbenes and other minor polyphenol subclasses. Similar null results were found in the US case–control study of lignans.[27] In EPIC, we have previously studied the association between coffee consumption, the main food contributor to phenolic acids[11] and TC risk, and these findings were not significant either.[25]

In the present study, a diet high in anthocyanidins and theaflavins and low in hydroxycinnamic acids, alkylmethoxyphenols and methoxyphenols was related to a decreased follicular TC risk using the quartiles of exposure, but they were not consistent with the results using the continuous variable or after the Bonferroni correction. The main food source of hydroxycinnamic acids, alkylmethoxyphenols and methoxyphenols is coffee,[11] which was not related to follicular TC risk in a previous EPIC study.[25] Tea is the only food source of theaflavins,[11] and tea was borderline statistically and inversely associated with follicular TC risk in the EPIC study.[25] Furthermore, it is difficult to explain the biological plausibility of these opposite associations with tea and coffee polyphenols.

After stratification by BMI, we observed a suggestive inverse association between the intake of polyphenols, especially phenolic acids, and differentiated TC, particularly papillary TC, in subjects with BMI ≥ 25, but not in those with BMI < 25. In our previous study, weaker associations were also found with coffee consumption in obese individuals.[25] Obesity is a low-grade inflammation disease,[28] and excess adiposity[18] and inflammation[29] are risk factors for TC confirmed previously in the EPIC study. Furthermore, polyphenols have anti-inflammatory[30] and anti-obesity[31] effects. Thus, we hypothesize that polyphenols may counteract the unfavorable chronic inflammatory profile in overweight and obese subjects against differentiated TC risk. Further studies are needed to investigate these potential relationships in subjects with BMI ≥ 25.

In summary, although polyphenols may have some anticarcinogenic activities in certain cancer sites,[1,3,4] our large prospective study did not support an association between the intake of any polyphenol class and differentiated TC risk in Europe. Despite these overall null results, a possible inverse association was observed in subjects with BMI ≥ 25, which might be related to the anti-inflammatory and anti-obesity properties of polyphenols. These potential associations and mechanisms should be further investigated.

Acknowledgements

The authors thank Bertrand Hémon for his valuable help with the European Prospective Investigation into Cancer and Nutrition (EPIC) database. This study was supported by the Institute of Health Carlos III, Spain (CP15/00100), and cofounded by the European Regional Development Fund (ERDF) "A way to build Europe." The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); 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), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); European Research Council (ERC-2009-AdG 232997); Health Research Fund (FIS): PI13/00061 to Granada; PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, AGAUR - Generalitat de Catalunya (exp. 2014 SGR 726), The Health Research Funds RD12/0036/0018, cofounded by European Regional Development Fund (ERDF) "A way to build Europe (Spain)"; Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom). We thank CERCA Programme/Generalitat de Catalunya for institutional support. R.Z.-R. was supported by the "Miguel Servet" program (CP15/00100) from the Institute of Health Carlos III and European Social Fund (ESF).

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