

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

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KEY WORDS: Polyphenols, flavonoids, intake, thyroid cancer, cohort, EPIC

LIST OF ABBREVIATIONS: BMI, body mass index; TC, thyroid cancer; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and

Nutrition; HR, hazard ratio; ICD, International Classification of Diseases; NOS, not otherwise specified; SD, standard deviation.

AVAILABILITY OF DATA AND MATERIALS:

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>.

NOVELTY & IMPACT:

In this large prospective study, no associations were observed between dietary polyphenol intake and differentiated thyroid cancer risk; although further studies are warranted to investigate the potential protective associations in overweight and obese individuals.

1 ABSTRACT

2 Polyphenols are bioactive compounds with several anticarcinogenic activities;
3 however, human data regarding associations with thyroid cancer (TC) is still
4 negligible. Our aim was to evaluate the association between intakes of total,
5 classes and subclasses of polyphenols and risk of differentiated TC and its
6 main subtypes, papillary and follicular, in a European population. The European
7 Prospective Investigation into Cancer and Nutrition (EPIC) cohort included
8 476,108 men and women from 10 European countries. During a mean follow-up
9 of 14 years, there were 748 incident differentiated TC cases, including 601
10 papillary and 109 follicular tumours. Polyphenol intake was estimated at
11 baseline using validated centre/country specific dietary questionnaires and the
12 Phenol-Explorer database. In multivariable-adjusted Cox regression models, no
13 association between total polyphenol and the risks of overall differentiated TC
14 ($HR_{Q4 \text{ vs } Q1} = 0.99$, 95% CI 0.77 - 1.29), papillary ($HR_{Q4 \text{ vs } Q1} = 1.06$, 95% CI 0.80
15 - 1.41), or follicular TC ($HR_{Q4 \text{ vs } Q1} = 1.10$, 95% CI 0.55 – 2.22) were found. No
16 associations were observed either for flavonoids, phenolic acids or the rest of
17 classes and subclasses of polyphenols. After stratification by body mass index
18 (BMI), an inverse association between the intake of polyphenols (P-
19 trend=0.019) and phenolic acids (P-trend=0.007) and differentiated TC risk in
20 subjects with $BMI \geq 25$ was observed. In conclusion, our study showed no
21 associations between dietary polyphenol intake and differentiated TC risk;
22 although further studies are warranted to investigate the potential protective
23 associations 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 defence 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⁻

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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 intake¹¹ 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 on-going multi-centre 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 (IARC). Participants were excluded from the analyses if they had a previous cancer other than non-melanoma 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 figure 1**).

Identification and follow-up of thyroid cancer 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 centres, 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 section “Subjects and study design”. Poorly differentiated TC (e.g. anaplastic (n = 9), medullary (n = 37), lymphoma (n = 1) or “other morphologies” (n = 5)) were also excluded (Supplementary figure 1). Thus, we only included differentiated TC, i.e. papillary (n=601), follicular (n=109) and not otherwise specified TC (n=38) which are also likely to be papillary tumours. Data on the stage of differentiated TC at diagnosis were collected from each centre, where possible. A total of 468 cases (63%) had stage information, of which 371 were classified as low-risk (tumour-node-metastasis [TNM] staging score of T1-T2) and 97 were classified as high-risk tumours (T3-T4).

Dietary assessment and data collection

Habitual diet of the preceding year was collected using a validated country/centre-specific dietary questionnaire at baseline.^{12,13} Most centres utilized a self-administered food frequency questionnaire. In the remaining centres (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 non-quantitative 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 centres. In EPIC-Oxford, Norway and France, anthropometric measurements were self-reported.¹²

Statistical analysis

Hazard ratios (HR) and 95% confidence intervals (CIs) for the associations between total, 4 classes and 22 subclasses (see 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 analysed as sex-specific quartiles using both absolute intakes (mg/d) and intakes adjusted for energy as density variables (mg/2000kcal*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 analysed as continuous variables, after log₂ transformation to improve normality of intake distributions. Model 1 was

stratified by EPIC study centre, sex and age at recruitment (1-year interval). Model 2 was additionally adjusted for potential confounders, i.e., variables associated with TC risk in previous EPIC works¹⁸⁻²¹: 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 fibre (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. ≥15g/d; and for men <30 vs. ≥30g/d), and BMI (<25 vs. ≥25kg/m²) 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 (RERI).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 tumour (T3-T4) cases, as a way to control for potential over-diagnosis. We also conducted two sensitivity models, excluding 77 cases who 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 2-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).

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 tumours. The highest median of total polyphenol intakes was in Denmark (1,573mg/d); whereas the lowest intake was 653mg/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 (**Supplementary table 1**) and multivariable models (**Table 2**), total polyphenol intake was not associated with the risk of differentiated TC using either absolute amounts ($HR_{Q4 \text{ vs } Q1} = 0.99$, 95 % CI 0.77 - 1.29; p-trend =0.97) (**Table 2**) or nutrient density ($HR_{Q4 \text{ vs } Q1} = 1.01$, 95 % CI 0.79 - 1.29; p-trend =0.71) (**Supplementary table 2**). No associations were observed in any cancer subtype: papillary ($HR_{Q4 \text{ vs } Q1} = 1.06$, 95 % CI 0.80 - 1.41; p-trend =0.55) and follicular tumours ($HR_{Q4 \text{ vs } Q1} = 1.10$, 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 fibre 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 ($HR_{Q4 \text{ vs } Q1} = 1.00$, 95 % CI 0.77 - 1.32; p-trend =0.91); in either high ($HR_{Q4 \text{ vs } Q1} = 0.98$, 95 % CI 0.74 - 1.29; p-trend =0.87) or low TC incidence rate EPIC countries ($HR_{Q4 \text{ vs } Q1} = 0.99$, 95 % CI 0.55 - 1.77; p-trend =0.95); and in either low risk ($HR_{Q4 \text{ vs } Q1} = 1.00$, 95 % CI 0.70 -

1.43; p-trend =0.96) or high risk tumours ($HR_{Q4 \text{ vs } Q1} = 1.23$, 95 % CI 0.60 - 2.51; p-trend =0.22) (Supplementary table 2). In the sensitivity analysis, excluding TC cases diagnosed in the first 2 years of follow-up ($HR_{Q4 \text{ vs } Q1} = 0.97$, 95 % CI 0.74 - 1.27; p-trend =0.84) (Supplementary table 2), 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 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 < 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) (**Supplementary figure 2**).

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

This study has some limitations. Firstly, although we have used centre/country-specific validated dietary questionnaires¹³ 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. Secondly, dietary and lifestyle data was 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 over-diagnosis 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 pre-diagnostic 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 US, 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 group²⁴ or tea,²⁵ which are the main food sources of flavan-3-ol 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 \geq 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 disease²⁸, and excess adiposity¹⁸ and inflammation²⁹ are risk factors for TC confirmed previously in the EPIC study. Furthermore, polyphenols have anti-inflammatory³⁰ and anti-obesity³¹ effects. Thus, we hypothesize that polyphenols may counteract the unfavourable 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 \geq 25.

In summary, although polyphenols may have some anti-carcinogenic 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 \geq 25, which might be related to the anti-

293 inflammatory and anti-obesity properties of polyphenols. These potential
294 associations and mechanisms should be further investigated.

CONFLICT OF INTEREST:

The authors are not aware of any conflicts of interest.

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DISCLAIMER:

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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AUTHORS' CONTRIBUTIONS

R.Z.-R. designed the research; V.C. performed the statistical analysis; R.Z.-R. drafted the manuscript; S.F. and S.R. had primary responsibility for final content; S.F., C.K., E.W., J.H., M.S., A.T., A.O., K.O., M.-C.B.-R., T.T., F.R.M., V.K., T.K., H.B., A.T., A.K., G.M., D.P., V.K., S.P., R.T., C.S., C.L., M.R.-B., P.A., S.M.C.-Y., E.A., M.A., U.E., H.B.B.-de-M., R.V., J.A.S., G.B., A.S., A.A., S.R. contributed to the design of the study, data collection, and quality control

341 and analysis. All authors read, critically reviewed and approved the final
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REFERENCE LIST

1. Zamora-Ros R, Touillaud M, Rothwell JA, Romieu I, Scalbert A. Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: current tools and applications and their limits. *Am J Clin Nutr* 2014;100:11-26.
2. van Dam RM, Naidoo N, Landberg R. Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings. *Curr Opin Lipidol* 2013;24:25-33.
3. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid Redox Signal* 2013;18:1818-92.
4. Grosso G, Godos J, Lamuela-Raventos R, Ray S, Micek A, Pajak A, Sciacca S, D'Orazio N, Del Rio D, Galvano F. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. *Mol Nutr Food Res* 2017;61.
5. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. *N Engl J Med* 2016;375:614-7.
6. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. *J Cancer Epidemiol* 2013;2013:965212.
7. Kitahara CM, McCullough ML, Franceschi S, Rinaldi S, Wolk A, Neta G, Olov Adami H, Anderson K, Andreotti G, Beane Freeman LE, Bernstein L, Buring JE, Clavel-Chapelon F, De Roo LA, Gao YT, Gaziano JM, Giles GG, Håkansson N, Horn-Ross PL, Kirsh VA, Linet MS, MacInnis RJ, Orsini N, Park Y, Patel AV, Purdue MP, Riboli E, Robien K, Rohan T, Sandler DP, Schairer C, Schneider AB, Sesso HD, Shu XO, Singh PN, van den Brandt PA, Ward E, Weiderpass E, White E, Xiang YB, Zeleniuch-Jacquotte A, Zheng W, Hartge P, Berrington de González A. Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective Studies. *Thyroid* 2016;26:306-18.
8. Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, Berrington de González A. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* 2010;171:242-52.
9. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. *Cancer Causes Control* 2009;20:75-86.

10. Xiao Q, Park Y, Hollenbeck AR, Kitahara CM. Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP diet and health study. *Cancer Epidemiol Biomarkers Prev* 2014;23:1102-8.
11. Zamora-Ros R, Knaze V, Rothwell JA, Hémon B, Moskal A, Overvad K, Tjønneland A, Kyrø C, Fagherazzi G, Boutron-Ruault MC, Touillaud M, Katzke V, Kühn T, Boeing H, Förster J, Trichopoulou A, Valanou E, Peppas E, Palli D, Agnoli C, Ricceri F, Tumino R, de Magistris MS, Peeters PH, Bueno-de-Mesquita HB, Engeset D, Skeie G, Hjartåker A, Menéndez V, Agudo A, Molina-Montes E, Huerta JM, Barricarte A, Amiano P, Sonestedt E, Nilsson LM, Landberg R, Key TJ, Khaw KT, Wareham NJ, Lu Y, Slimani N, Romieu I, Riboli E, Scalbert A. Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Nutr* 2015;55:1359-75.
12. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, Overvad K, Tjønneland A, Clavel-Chapelon F, Thiébaud A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-De-Mesquita HB, Peeters PH, Lund E, Engeset D, González CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5(6B):1113-24.
13. Margetts BM, Pietinen P. European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. *Int J Epidemiol* 1997;26 Suppl 1:S1-S5.
14. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, Salvini S, Parpinel M, Møller A, Ireland J, Becker W, Farran A, Westenbrink S, Vasilopoulou E, Unwin J, Borgejordet A, Rohrmann S, Church S, Gnagnarella P, Casagrande C, van Bakel M, Niravong M, Boutron-Ruault MC, Stripp C, Tjønneland A, Trichopoulou A, Georga K, Nilsson S, Mattisson I, Ray J, Boeing H, Ocké M, Peeters PH, Jakszyn P, Amiano P, Engeset D, Lund E, de Magistris MS, Sacerdote C, Welch A, Bingham S, Subar AF, Riboli E. 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.
15. Neveu V, Perez-Jimenez J, Vos F, Crespy V, du Chaffaut L, Mennen L, Mennen L, Knox C, Eisner R, Cruz J, Wishart D, Scalbert A. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database (Oxford)* 2010;2010:bap024.
16. Rothwell JA, Perez-Jimenez J, Neveu V, Medina-Remón A, M'hiri N, García-Lobato P, Manach C, Knox C, Eisner R, Wishart DS, Scalbert A. The Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. *Database (Oxford)* 2013;bat070.

17. Knaze V, Rothwell JA, Zamora-Ros R, Moskal A, Kyrø C, Jakszyn P, Skeie G, Weiderpass E, Santucci de Magistris M, Agnoli C, Westenbrink S, Sonestedt E, Trichopoulou A, Vasilopoulou E, Peppas E, Ardanaz E, Huerta JM, Boeing H, Mancini FR, Scalbert A, Slimani N. A new food-composition database for 437 polyphenols in 19,899 raw and prepared foods used to estimate polyphenol intakes in adults from 10 European countries. *Am J Clin Nutr* 2018;108:517-24.
18. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, Tjønneland A, Halkjær J, Lukanova A, Kaaks R, Bergmann MM, Boeing H, Trichopoulou A, Zylis D, Valanou E, Palli D, Agnoli C, Tumino R, Polidoro S, Mattiello A, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Lund E, Skeie G, Rodríguez L, Travier N, Sánchez MJ, Amiano P, Huerta JM, Ardanaz E, Rasmuson T, Hallmans G, Almquist M, Manjer J, Tsilidis KK, Allen NE, Khaw KT, Wareham N, Byrnes G, Romieu I, Riboli E, Franceschi S. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* 2012;131:E1004-E1014.
19. Sen A, Tsilidis KK, Allen NE, Rinaldi S, Appleby PN, Almquist M, Schmidt JA, Dahm CC, Overvad K, Tjønneland A, Rostgaard-Hansen AL, Clavel-Chapelon F, Baglietto L, Boutron-Ruault MC, Kühn T, Katze VA, Boeing H, Trichopoulou A, Tsironis C, Lagiou P, Palli D, Pala V, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HA, Peeters PH, Hjartåker A, Lund E, Weiderpass E, Quirós JR, Agudo A, Sánchez MJ, Arriola L, Gavrila D, Gurrea AB, Tosovic A, Hennings J, Sandström M, Romieu I, Ferrari P, Zamora-Ros R, Khaw KT, Wareham NJ, Riboli E, Gunter M, Franceschi S. Baseline and lifetime alcohol consumption and risk of differentiated thyroid carcinoma in the EPIC study. *Br J Cancer* 2015;113:840-7.
20. Zamora-Ros R, Rinaldi S, Biessy C, Tjønneland A, Halkjaer J, Fournier A, Boutron-Ruault MC, Mesrine S, Tikk K, Fortner RT, Boeing H, Förster J, Trichopoulou A, Trichopoulos D, Papatesta EM, Masala G, Tagliabue G, Panico S, Tumino R, Polidoro S, Peeters PH, Bueno-de-Mesquita HB, Weiderpass E, Lund E, Argüelles M, Agudo A, Molina-Montes E, Navarro C, Barricarte A, Larrañaga N, Manjer J, Almquist M, Sandström M, Hennings J, Tsilidis KK, Schmidt JA, Khaw KT, Wareham NJ, Romieu I, Byrnes G, Gunter MJ, Riboli E, Franceschi S. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: The EPIC study. *Int J Cancer* 2015;136:1218-27.
21. Zamora-Ros R, Rinaldi S, Tsilidis KK, Weiderpass E, Boutron-Ruault MC, Rostgaard-Hansen AL, Tjønneland A, Clavel-Chapelon F, Mesrine S, Katzke VA, Kühn T, Förster J, Boeing H, Trichopoulou A, Lagiou P, Klinaki E, Masala G, Sieri S, Ricceri F, Tumino R, Mattiello A, Peeters PH, Bueno-de-Mesquita HB, Engeset D, Skeie G, Argüelles M, Agudo A, Sánchez MJ, Chirlaque MD, Barricarte A, Chamosa S, Almquist M, Tosovic A, Hennings J, Sandström M, Schmidt JA, Khaw KT, Wareham NJ, Cross AJ, Slimani N, Byrnes G, Romieu I, Riboli E, Franceschi S. Energy and macronutrient intake and risk of differentiated thyroid

- carcinoma in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer* 2016;138:65-73.
22. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. 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. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Lippincott Williams & Wilkins, 2008.
 24. Zamora-Ros R, Beraud V, Franceschi S, Cayssials V, Tsilidis KK, Boutron-Ruault MC, Weiderpass E, Overvad K, Tjønneland A, Eriksen AK, Bonnet F, Affret A, Katzke V, Kühn T, Boeing H, Trichopoulou A, Valanou E, Karakatsani A, Masala G, Grioni S, Santucci de Magistris M, Tumino R, Ricceri F, Skeie G, Parr CL, Merino S, Salamanca-Fernández E, Chirlaque MD, Ardanaz E, Amiano P, Almquist M, Drake I, Hennings J, Sandström M, Bueno-de-Mesquita HBA, Peeters PH, Khaw KT, Wareham NJ, Schmidt JA, Perez-Cornago A, Aune D, Riboli E, Slimani N, Scalbert A, Romieu I, Agudo A, Rinaldi S. Consumption of fruits, vegetables and fruit juices and differentiated thyroid carcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Int J Cancer* 2018;142:449-59.
 25. Zamora-Ros R, Alghamdi MA, Cayssials V, Franceschi S, Almquist M, Hennings J, Sandström M, Tsilidis KK, Weiderpass E, Boutron-Ruault MC, Hammer Bech B, Overvad K, Tjønneland A, Petersen KEN, Mancini FR, Mahamat-Saleh Y, Bonnet F, Kühn T, Fortner RT, Boeing H, Trichopoulou A, Bamia C, Martimianaki G, Masala G, Grioni S, Panico S, Tumino R, Fasanelli F, Skeie G, Braaten T, Lasheras C, Salamanca-Fernández E, Amiano P, Chirlaque MD, Barricarte A, Manjer J, Wallström P, Bueno-de-Mesquita HB, Peeters PH, Khaw KT, Wareham NJ, Schmidt JA, Aune D, Byrnes G, Scalbert A, Agudo A, Rinaldi S. Coffee and tea drinking in relation to the risk of differentiated thyroid carcinoma: results from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Nutr*. 2018 Dec 10 (Epub ahead of print; DOI: doi:10.1007/s00394-018-1874-z).
 26. Yeo Y, Ma SH, Hwang Y, Horn-Ross PL, Hsing A, Lee KE, Park YJ, Park DJ, Yoo KY, Park SK. Diabetes mellitus and risk of thyroid cancer: a meta-analysis. *PLoS One* 2014;9:e98135.
 27. Horn-Ross PL, Hoggatt KJ, Lee MM. Phytoestrogens and thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. *Cancer Epidemiol Biomarkers Prev* 2002;11:43-9.
 28. Pereira SS, Alvarez-Leite JI. Low-Grade Inflammation, Obesity, and Diabetes. *Curr Obes Rep* 2014;3:422-31.

29. Dossus L, Franceschi S, Biessy C, Navionis AS, Travis RC, Weiderpass E, Scalbert A, Romieu I, Tjønneland A, Olsen A, Overvad K, Boutron-Ruault MC, Bonnet F, Fournier A, Fortner RT, Kaaks R, Aleksandrova K, Trichopoulou A, La Vecchia C, Peppas E, Tumino R, Panico S, Palli D, Agnoli C, Vineis P, Bueno-de-Mesquita HBA, Peeters PH, Skeie G, Zamora-Ros R, Chirlaque MD, Ardanaz E, Sánchez MJ, Ramón Quirós J, Dorronsoro M, Sandström M, Nilsson LM, Schmidt JA, Khaw KT, Tsilidis KK, Aune D, Riboli E, Rinaldi S. Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study. *Int J Cancer* 2018;142:1332-42.
30. Pounis G, Bonaccio M, Di Castelnuovo A, Costanzo S, de Curtis A, Persichillo M, Sieri S, Donati MB, Cerletti C, de Gaetano G, Iacoviello L. Polyphenol intake is associated with low-grade inflammation, using a novel data analysis from the Moli-sani study. *Thromb Haemost* 2016;115:344-52.
31. Bertoia ML, Rimm EB, Mukamal KJ, Hu FB, Willett WC, Cassidy A. Dietary flavonoid intake and weight maintenance: three prospective cohorts of 124,086 US men and women followed for up to 24 years. *BMJ*. 2016;352:i17.

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	838-1149	1150-1539	1540-9521
Polyphenol (mg/d), women		14-738	739-1053	1054-1460	1460-10615
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 (y), 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)	2075 (619)	1811 (543)	2022 (571)	2145 (602)	2321 (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*, %					
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*, yes, %	57.2	48.9	55.3	61.0	63.5
Infertility problems*, yes, %	3.1	2.5	2.7	3.3	3.9

Abbreviations: p25 and p75: percentile 25th and 75th.

*Only in women (N=333876, 70.1%)

¹Missing values (classified as not specified): smoke status (n=9676; 2.0%), education level (n=16929; 3.6%), physical activity (n=8824; 1.9%), diabetes (38970; 8.2%), ever use of oral contraceptive (n=8,427; 2.5%), infertility problems (n=111,162; 33.3%)

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.

Polyphenol classes and subclasses	Intake (mg/d)	Overall TC risk					Continuous (log2)
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
Polyphenols	1083.3 (767.1-1485.0)	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)
Flavan3ols	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 [#]	1.5 (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)
Flavanols	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 [#]	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)

[#]classified as non-consumers and tertiles of consumers

*P-value<0.05; **P-value<0.01; no associations exceed the Bonferroni threshold ($P < 0.05/26 = 0.002$)

¹P-value for heterogeneity for papillary vs follicular cancer using the Wald test

Cox model was stratified by sex, age and centre, 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

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.

Polyphenol classes and subclasses	Papillary TC risk						Follicular TC risk						P for heterogeneity
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	Continuous	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
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
Flavan3ols	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 (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 (1.00-1.74)	1.31 (0.97-1.77)	1.13 (0.79-1.61)	0.52	0.96 (0.91-1.01)	1 (ref)	0.86 (0.50-1.45)	0.60 (0.31-1.13)	0.54 (0.23-1.25)	0.13	0.98 (0.87-1.10)	0.09

		1.75)*		1.63)		1.01)		1.47)	1.16)	1.28)		1.10)	
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 (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

[#]classified as non-consumers and tertiles of consumers

*P-value<0.05; **P-value<0.01; no associations exceed the Bonferroni threshold (P<0.05/26) = 0.002

¹P-value for heterogeneity for papillary vs follicular cancer using the Wald test

Cox model was stratified by sex, age and centre, and additionally adjusted for smoking status, education level, body mass index (kg/m²), 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

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							P-interaction
	N 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)	N 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)	
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

*P-value<0.05; **P-value<0.01; no associations exceed the Bonferroni threshold ($P < 0.05/26$) = 0.002

Cox model was stratified by sex, age and centre, 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

Supplementary table 1. Hazard ratios (95% CIs) of the associations between polyphenol classes and the risk of overall, papillary and follicular thyroid cancers in the EPIC study.

Polyphenol classes and subclasses	Overall TC risk					P-trend	Continuous (log2)
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
Polyphenols	1 (ref)	0.84 (0.68-1.03)	0.86 (0.69-1.08)	0.94 (0.74-1.19)	0.82	0.95 (0.84-1.07)	
Flavonoids	1 (ref)	1.08 (0.87-1.33)	1.13 (0.90-1.41)	0.99 (0.77-1.28)	0.79	1.01 (0.93-1.11)	
Flavanols	1 (ref)	1.01 (0.81-1.25)	1.25 (1.00-1.57)	0.92 (0.70-1.20)	0.78	1.00 (0.93-1.07)	
Flavan3ols	1 (ref)	1.17 (0.94-1.45)	1.19 (0.94-1.50)	1.02 (0.77-1.34)	0.82	1.00 (0.95-1.05)	
Proanthocyanidins	1 (ref)	1.02 (0.82-1.26)	1.03 (0.83-1.29)	1.07 (0.84-1.35)	0.59	1.01 (0.93-1.09)	
Theaflavins [#]	1 (ref)	1.10 (0.89-1.36)	1.23 (1.00-1.52)	0.81 (0.60-1.10)	0.98	1.00 (1.00-1.01)	
Flavanols	1 (ref)	1.06 (0.86-1.31)	1.07 (0.85-1.35)	0.90 (0.68-1.18)	0.56	0.97 (0.89-1.05)	
Flavanones	1 (ref)	1.08 (0.88-1.33)	1.21 (0.98-1.49)	1.18 (0.95-1.46)	0.08	1.04 (0.99-1.08)	
Anthocyanins	1 (ref)	1.00 (0.79-1.27)	0.94 (0.74-1.19)	0.98 (0.77-1.26)	0.81	0.97 (0.93-1.01)	
Flavones	1 (ref)	1.09 (0.86-1.37)	1.08 (0.85-1.36)	1.19 (0.94-1.52)	0.18	1.06 (0.98-1.16)	
Dihydrochalcones	1 (ref)	1.09 (0.89-1.34)	1.20 (0.97-1.48)	1.06 (0.84-1.33)	0.38	1.00 (0.98-1.02)	
Dihydroflavonols	1 (ref)	0.92 (0.74-1.16)	0.91 (0.73-1.12)	0.79 (0.64-0.97)*	0.03	0.99 (0.98-1.00)	
Isoflavonoids	1 (ref)	0.96 (0.78-1.19)	0.95 (0.76-1.18)	0.93 (0.71-1.21)	0.56	0.98 (0.96-1.00)*	
Phenolic acids	1 (ref)	0.77 (0.62-0.94)*	0.71 (0.57-0.89)**	0.97 (0.78-1.20)	0.96	0.94 (0.87-1.02)	
Hydroxycinnamic	1 (ref)	0.80 (0.65-0.98)*	0.74 (0.59-0.92)**	1.02 (0.83-1.25)	0.94	0.96 (0.90-1.03)	
Hydroxybenzoics	1 (ref)	1.05 (0.83-1.33)	1.10 (0.86-1.42)	0.93 (0.69-1.25)	0.72	0.99 (0.94-1.04)	
Hydroxyphenylacetic	1 (ref)	0.96 (0.78-1.17)	0.83 (0.67-1.02)	0.73 (0.59-0.90)**	0.001	0.96 (0.94-0.98)**	
Stilbenes	1 (ref)	1.27 (1.02-1.59)*	1.12 (0.89-1.40)	0.93 (0.74-1.16)	0.20	0.98 (0.95-1.01)	
Lignans	1 (ref)	0.94 (0.75-1.17)	1.00 (0.80-1.25)	0.82 (0.64-1.05)	0.20	0.94 (0.85-1.04)	
Other polyphenols							
Alkylphenols	1 (ref)	1.04 (0.84-1.28)	1.10 (0.87-1.40)	0.83 (0.62-1.12)	0.48	0.96 (0.91-1.01)	
Tyrosols	1 (ref)	1.15 (0.90-1.47)	1.05 (0.82-1.35)	0.81 (0.61-1.08)	0.12	0.94 (0.91-0.98)**	
Alkylmethoxyphenols	1 (ref)	0.78 (0.64-0.96)*	0.75 (0.60-0.94)*	1.07 (0.87-1.32)	0.69	0.99 (0.96-1.01)	
Methoxyphenols	1 (ref)	0.77 (0.62-0.94)*	0.69 (0.55-0.87)**	1.05 (0.85-1.28)	0.96	0.99 (0.97-1.00)	
Hydroxybenzaldehydes [#]	1 (ref)	0.86 (0.68-1.08)	0.83 (0.66-1.04)	0.81 (0.65-1.01)	0.08	0.96 (0.93-0.98)**	
Hydroxyphenylpropenes [#]	1 (ref)	1.17 (0.90-1.51)	0.95 (0.73-1.23)	1.00 (0.68-1.46)	0.60	1.00 (0.99-1.01)	
Hydroxycoumarins	1 (ref)	1.02 (0.83-1.26)	0.98 (0.78-1.21)	0.73 (0.57-0.94)*	0.02	0.99 (0.98-1.01)	
Furanocoumarins	1 (ref)	1.08 (0.85-1.37)	1.26 (0.99-1.59)	0.85 (0.65-1.11)	0.50	0.99 (0.98-1.01)	

Polyphenol classes and subclasses	Papillary TC risk					Continuous (log2)
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
Polyphenols	1 (ref)	0.84 (0.67-	0.93 (0.72-	1.01 (0.77-	0.68	0.97 (0.85-

		1.07)	1.19)	1.31)		1.10)
Flavonoids	1 (ref)	1.09 (0.86-1.40)	1.26 (0.98-1.62)	1.10 (0.83-1.47)	0.58	1.06 (0.96-1.17)
Flavanols	1 (ref)	1.06 (0.83-1.36)	1.40 (1.09-1.80)*	1.03 (0.77-1.39)	0.28	1.03 (0.95-1.12)
Flavan3ols	1 (ref)	1.19 (0.93-1.52)	1.29 (0.99-1.68)	1.14 (0.84-1.55)	0.29	1.03 (0.98-1.09)
Proanthocyanidins	1 (ref)	1.01 (0.79-1.29)	1.12 (0.87-1.44)	1.10 (0.84-1.43)	0.37	1.04 (0.95-1.13)
Theaflavins [#]	1 (ref)	1.12 (0.88-1.42)	1.35 (1.07-1.71)**	0.89 (0.64-1.25)	0.38	1.01 (1.00-1.01)
Flavonols	1 (ref)	1.00 (0.78-1.28)	1.08 (0.84-1.39)	0.94 (0.69-1.27)	0.90	1.00 (0.91-1.10)
Flavanones	1 (ref)	1.13 (0.90-1.41)	1.22 (0.97-1.54)	1.16 (0.91-1.47)	0.18	1.03 (0.99-1.08)
Anthocyanins	1 (ref)	1.08 (0.83-1.43)	1.00 (0.76-1.31)	1.16 (0.87-1.54)	0.37	0.98 (0.94-1.03)
Flavones	1 (ref)	1.10 (0.85-1.43)	1.08 (0.83-1.40)	1.31 (1.00-1.72)	0.06	1.10 (1.00-1.22)
Dihydrochalcones	1 (ref)	1.01 (0.81-1.27)	1.15 (0.91-1.45)	1.11 (0.86-1.44)	0.25	1.00 (0.97-1.02)
Dihydroflavonols	1 (ref)	0.93 (0.72-1.19)	0.90 (0.71-1.14)	0.80 (0.63-1.00)	0.05	0.99 (0.98-1.00)
Isoflavonoids	1 (ref)	0.88 (0.70-1.11)	0.89 (0.70-1.13)	0.95 (0.71-1.27)	0.64	0.98 (0.96-1.00)
Phenolic acids	1 (ref)	0.71 (0.57-0.90)**	0.68 (0.53-0.87)**	0.90 (0.72-1.14)	0.67	0.93 (0.85-1.01)
Hydroxycinnamic	1 (ref)	0.73 (0.58-0.92)**	0.64 (0.50-0.83)**	0.95 (0.76-1.19)	0.49	0.94 (0.87-1.02)
Hydroxybenzoics	1 (ref)	1.06 (0.81-1.39)	1.21 (0.91-1.62)	1.07 (0.77-1.50)	0.52	1.02 (0.96-1.08)
Hydroxyphenylacetic	1 (ref)	0.98 (0.78-1.23)	0.83 (0.66-1.05)	0.71 (0.56-0.90)**	0.002	0.96 (0.93-0.98)**
Stilbenes	1 (ref)	1.40 (1.09-1.80)*	1.19 (0.93-1.54)	0.98 (0.76-1.27)	0.36	0.98 (0.95-1.01)
Lignans	1 (ref)	1.01 (0.79-1.29)	1.02 (0.79-1.31)	0.86 (0.65-1.13)	0.31	0.96 (0.86-1.08)
Other polyphenols						
Alkylphenols	1 (ref)	1.07 (0.85-1.34)	1.13 (0.86-1.47)	0.72 (0.51-1.02)	0.29	0.96 (0.91-1.02)
Tyrosols	1 (ref)	1.26 (0.95-1.67)	1.17 (0.88-1.56)	0.93 (0.67-1.27)	0.45	0.94 (0.90-0.98)**
Alkylmethoxyphenols	1 (ref)	0.79 (0.63-1.00)	0.70 (0.54-0.90)*	1.02 (0.81-1.28)	0.83	0.98 (0.95-1.01)
Methoxyphenols	1 (ref)	0.70 (0.56-0.88)**	0.59 (0.45-0.76)**	0.98 (0.79-1.22)	0.55	0.98 (0.97-1.00)
Hydroxybenzaldehydes	1 (ref)	0.85 (0.66-1.10)	0.82 (0.63-1.06)	0.79 (0.62-1.01)	0.08	0.96 (0.93-0.99)**
Hydroxyphenylpropenes [#]	1 (ref)	1.23 (0.93-1.62)	0.97 (0.73-1.29)	1.11 (0.71-1.72)	0.82	1.00 (0.99-1.02)
Hydroxycoumarins	1 (ref)	1.02 (0.81-1.28)	0.92 (0.72-1.17)	0.71 (0.54-0.94)*	0.01	0.99 (0.97-1.01)
Furanocoumarins	1 (ref)	1.04 (0.80-1.35)	1.24 (0.96-1.61)	0.82 (0.61-1.09)	0.40	1.00 (0.98-1.02)

		Follicular TC risk				Continuous (log2)
		Quartile 1 HR (95% CI)	Quartile 2 HR (95% CI)	Quartile 3 HR (95% CI)	Quartile 4 HR (95% CI)	
Polyphenols	1 (ref)	0.98 (0.57-1.68)	0.78 (0.43-1.42)	0.94 (0.49-1.79)	0.78	0.94 (0.68-1.30)
Flavonoids	1 (ref)	0.89 (0.53-1.50)	0.67 (0.38-1.18)	0.64 (0.34-1.22)	0.14	0.83 (0.67-1.03)
Flavanols	1 (ref)	0.72 (0.43-1.23)	0.72 (0.42-1.25)	0.49 (0.25-0.98)*	0.06	0.87 (0.78-0.98)*
Flavan3ols	1 (ref)	0.86 (0.51-1.46)	0.61 (0.35-1.09)	0.50 (0.25-1.00)	0.02	0.86 (0.78-0.94)**
Proanthocyanidins	1 (ref)	1.05 (0.62-1.78)	0.50 (0.26-0.96)*	1.03 (0.57-1.85)	0.59	0.91 (0.80-1.03)
Theaflavins [#]	1 (ref)	0.80 (0.47-1.37)	0.60 (0.33-1.09)	0.40 (0.18-0.90)*	0.02	0.98 (0.96-1.00)*

Flavonols	1 (ref)	0.91 (0.54-1.54)	0.95 (0.55-1.66)	0.59 (0.29-1.21)	0.24	0.87 (0.76-0.99)*
Flavanones	1 (ref)	0.95 (0.55-1.65)	1.18 (0.68-2.02)	1.33 (0.77-2.30)	0.23	1.11 (0.99-1.24)
Anthocyanins	1 (ref)	0.55 (0.31-0.97)*	0.65 (0.38-1.11)	0.38 (0.20-0.70)**	0.01	0.93 (0.86-1.00)
Flavones	1 (ref)	0.91 (0.53-1.56)	0.85 (0.49-1.48)	0.59 (0.31-1.11)	0.12	0.93 (0.75-1.15)
Dihydrochalcones	1 (ref)	1.50 (0.85-2.65)	1.78 (1.02-3.10)*	0.84 (0.44-1.62)	0.89	1.00 (0.94-1.06)
Dihydroflavonols	1 (ref)	0.86 (0.49-1.52)	0.78 (0.45-1.37)	0.53 (0.30-0.96)*	0.04	0.99 (0.96-1.02)
Isoflavonoids	1 (ref)	1.78 (1.02-3.10)*	1.55 (0.84-2.85)	0.83 (0.38-1.79)	0.76	0.98 (0.94-1.02)
Phenolic acids	1 (ref)	1.14 (0.64-2.02)	1.02 (0.55-1.87)	1.75 (0.96-3.20)	0.07	1.12 (0.90-1.40)
Hydroxycinnamic	1 (ref)	1.50 (0.82-2.76)	1.52 (0.81-2.83)	2.24 (1.20-4.19)*	0.02	1.16 (0.95-1.42)
Hydroxybenzoics	1 (ref)	0.88 (0.51-1.49)	0.57 (0.31-1.06)	0.41 (0.19-0.87)*	0.01	0.84 (0.74-0.95)**
Hydroxyphenylacetic	1 (ref)	0.72 (0.43-1.20)	0.70 (0.42-1.19)	0.56 (0.32-0.99)*	0.048	0.96 (0.90-1.03)
Stilbenes	1 (ref)	0.78 (0.45-1.35)	0.77 (0.44-1.35)	0.50 (0.28-0.91)*	0.03	0.94 (0.88-1.01)
Lignans	1 (ref)	0.62 (0.35-1.09)	0.84 (0.48-1.46)	0.76 (0.40-1.44)	0.52	0.96 (0.73-1.27)
Other polyphenols						
Alkylphenols	1 (ref)	0.85 (0.45-1.59)	1.07 (0.54-2.10)	1.19 (0.58-2.46)	0.53	1.02 (0.88-1.19)
Tyrosols	1 (ref)	0.78 (0.46-1.31)	0.48 (0.26-0.88)*	0.37 (0.18-0.78)*	0.01	0.92 (0.85-1.00)
Alkylmethoxyphenols	1 (ref)	0.79 (0.44-1.42)	1.05 (0.59-1.88)	1.75 (0.99-3.09)	0.04	1.06 (0.96-1.17)
Methoxyphenols	1 (ref)	1.27 (0.70-2.31)	1.51 (0.83-2.73)	1.99 (1.08-3.66)*	0.020	1.02 (0.97-1.07)
Hydroxybenzaldehydes	1 (ref)	0.81 (0.45-1.48)	0.79 (0.44-1.42)	0.64 (0.36-1.16)	0.16	0.95 (0.89-1.02)
Hydroxyphenylpropenes*	1 (ref)	0.97 (0.42-2.28)	1.04 (0.47-2.31)	1.06 (0.42-2.68)	0.89	1.00 (0.96-1.03)
Hydroxycoumarins	1 (ref)	0.89 (0.50-1.57)	0.83 (0.46-1.50)	0.66 (0.35-1.25)	0.19	1.01 (0.96-1.06)
Furanocoumarins	1 (ref)	1.19 (0.65-2.19)	1.11 (0.58-2.15)	0.80 (0.37-1.74)	0.59	1.00 (0.95-1.04)

#classified as non-consumers and tertiles of consumers

*P-value<0.05; **P-value<0.01; no associations exceed the Bonferroni threshold ($P < 0.05/26 = 0.002$)

Cox model was stratified by sex, age and centre

Supplementary table 2. Hazard ratios (95% CIs) for thyroid cancer according to the intake of sex-specific quartiles of total polyphenols, flavonoids and phenolic acids in the sensitivity analysis in the EPIC study.

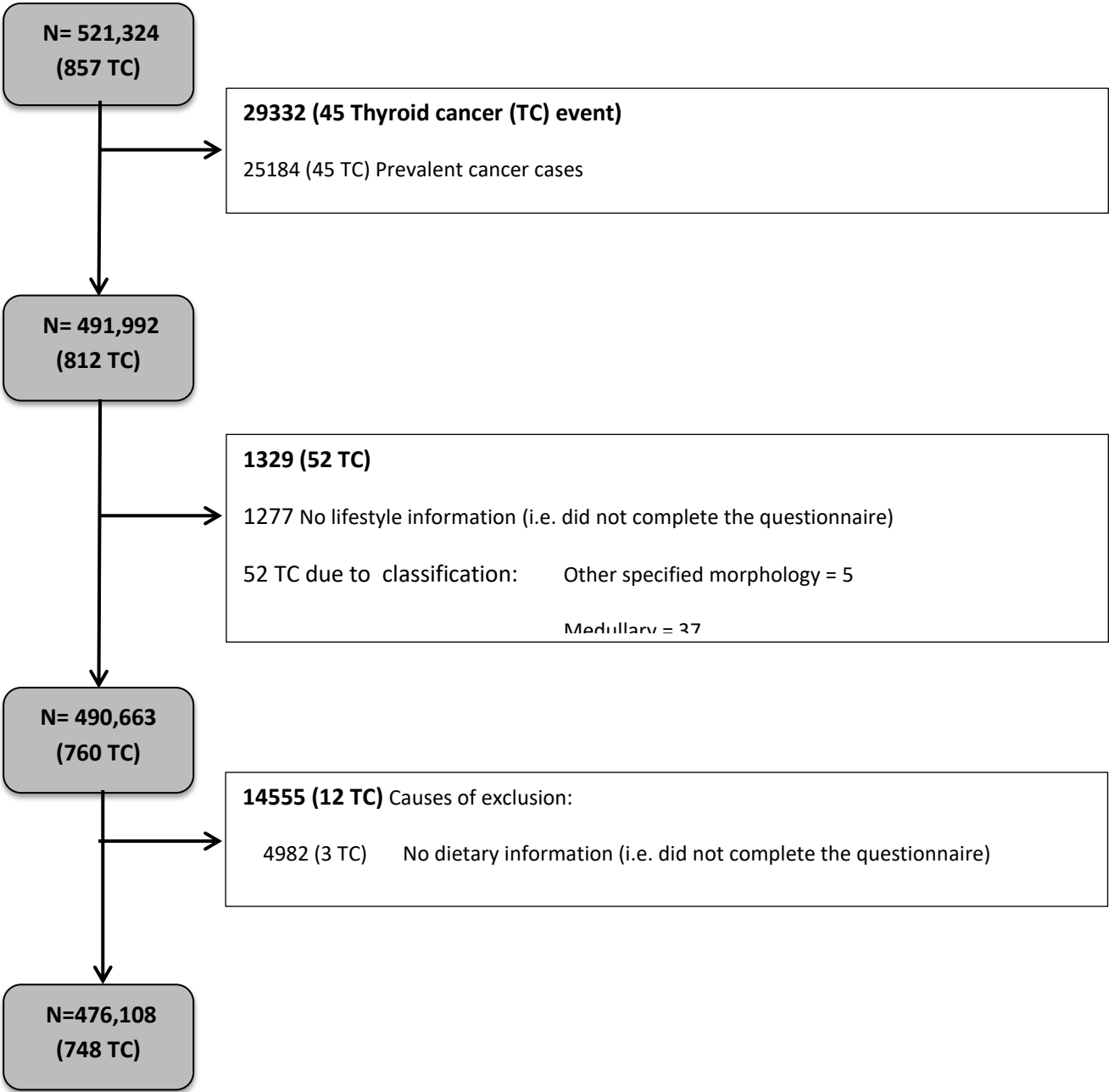
Overall TC risk					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
TC stages					
Low risk (T1-T2)					
Polyphenols	1 (ref)	0.91 (0.66 - 1.25)	0.88 (0.63 - 1.23)	1.00 (0.70 - 1.43)	0.96
Flavonoids	1 (ref)	1.09 (0.79 - 1.52)	1.06 (0.76 - 1.49)	1.09 (0.75 - 1.58)	0.76
Phenolic acids	1 (ref)	0.76 (0.56 - 1.05)	0.86 (0.62 - 1.19)	1.04 (0.77 - 1.40)	0.59
High risk (T3-T4)					
Polyphenols	1 (ref)	0.67 (0.33 - 1.36)	1.48 (0.77 - 2.84)	1.23 (0.60 - 2.51)	0.22
Flavonoids	1 (ref)	1.41 (0.72 - 2.75)	1.50 (0.76 - 2.97)	1.19 (0.55 - 2.57)	0.72
Phenolic acids	1 (ref)	1.16 (0.59 - 2.28)	1.15 (0.56 - 2.34)	1.90 (0.99 - 3.63)	0.05
TC incidence rate					
Countries with high incidence					
Polyphenols	1 (ref)	0.86 (0.67 - 1.09)	0.83 (0.63 - 1.07)	0.98 (0.74 - 1.29)	0.87
Flavonoids	1 (ref)	0.96 (0.75 - 1.22)	1.05 (0.81 - 1.35)	1.12 (0.85 - 1.48)	0.31
Phenolic acids	1 (ref)	0.80 (0.63 - 1.02)	0.75 (0.58 - 0.97)*	1.02 (0.79 - 1.31)	0.98
Countries with low incidence					
Polyphenols	1 (ref)	0.93 (0.60 - 1.46)	1.07 (0.64 - 1.81)	0.99 (0.55 - 1.77)	0.95
Flavonoids	1 (ref)	1.35 (0.87 - 2.08)	1.69 (1.01 - 2.83)*	1.22 (0.66 - 2.27)	0.37
Phenolic acids	1 (ref)	0.57 (0.36 - 0.88)*	0.71 (0.46 - 1.10)	0.78 (0.49 - 1.24)	0.36
Sensitivity analysis					
Nutrient density (mg/2000kcal*d)					
Polyphenols	1 (ref)	0.84 (0.68 - 1.03)	0.99 (0.79 - 1.23)	1.01 (0.79 - 1.29)	0.71
Flavonoids	1 (ref)	1.06 (0.86 - 1.31)	1.26 (1.01 - 1.56)*	1.02 (0.78 - 1.33)	0.35
Phenolic acids	1 (ref)	0.83 (0.67 - 1.02)	0.83 (0.67 - 1.04)	1.02 (0.82 - 1.27)	0.94
Women					

Polyphenols	1 (ref)	0.85 (0.68 - 1.07)	0.89 (0.69 - 1.14)	1.00 (0.77 - 1.32)	0.91
Flavonoids	1 (ref)	1.14 (0.91 - 1.44)	1.17 (0.91 - 1.50)	1.12 (0.83 - 1.50)	0.46
Phenolic acids	1 (ref)	0.76 (0.61 - 0.95)*	0.73 (0.57 - 0.92)**	1.01 (0.80 - 1.26)	0.91
Excluding TC cases diagnosed<2y					
Polyphenols	1 (ref)	0.90 (0.72 - 1.12)	0.92 (0.72 - 1.17)	0.97 (0.74 - 1.27)	0.84
Flavonoids	1 (ref)	1.11 (0.88 - 1.39)	1.25 (0.98 - 1.60)	1.07 (0.80 - 1.44)	0.40
Phenolic acids	1 (ref)	0.75 (0.61 - 0.94)*	0.68 (0.54 - 0.87)**	0.95 (0.75 - 1.19)	0.45

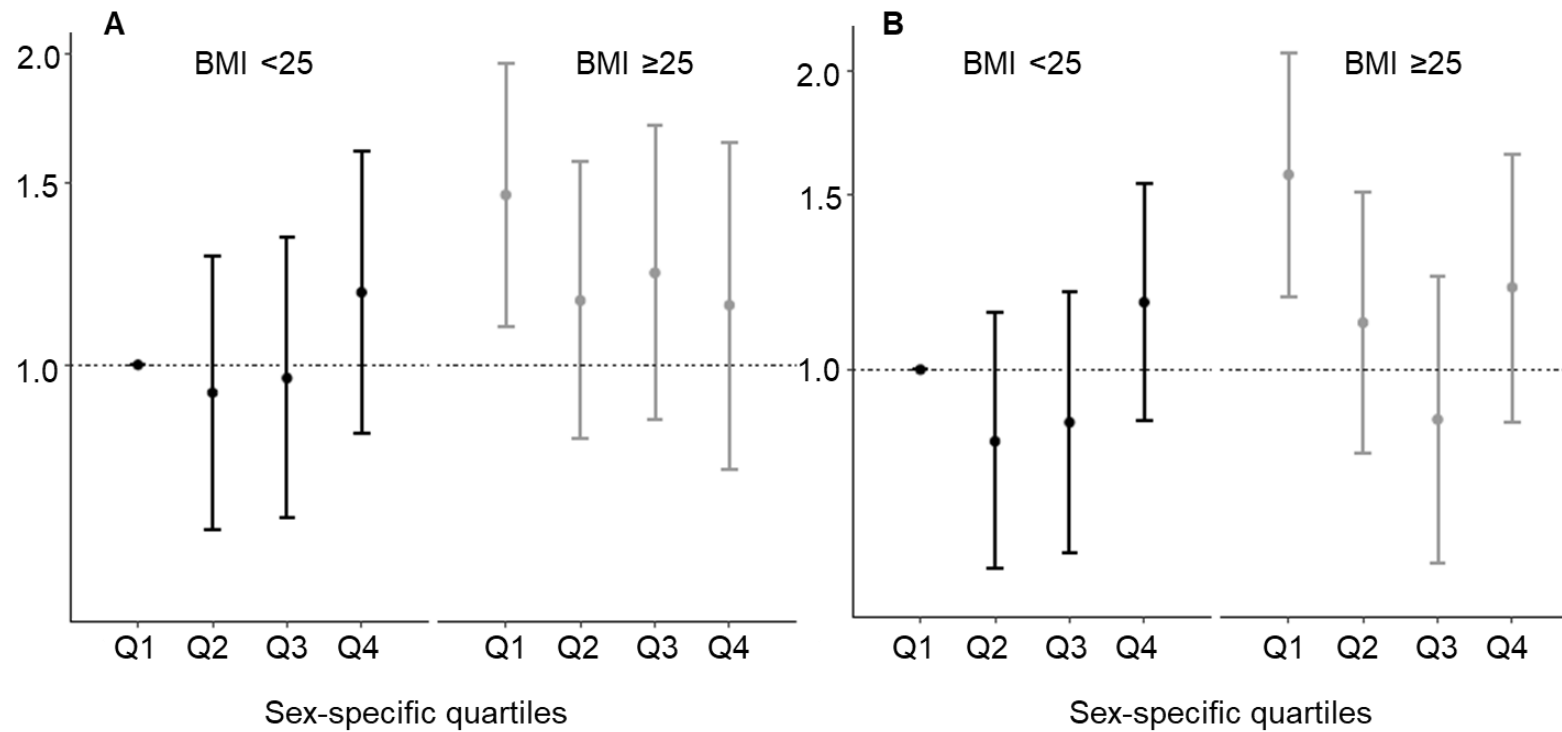
*P-value<0.05; **P-value<0.01

Cox model was stratified by sex, age and centre, and additionally adjusted for smoking status, education level, body mass index (kg/m²), 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

Supplementary figure 1: Participant flowchart



Supplementary figure 2. Hazard ratios (95% CIs) for differentiated thyroid cancer (TC) stratified by body mass index (BMI) according to the intake of quartiles of total polyphenols (A) and phenolic acids (B) in the EPIC study.



Relative Excess Risk due to Interaction (additive scale):

A) RERI Q4 vs Q1 (95% CI) = -0.49 (-1.05, 0.06); P for interaction = 0.08

B) RERI Q4 vs Q1 (95% CI) = -0.53 (-1.07, 0.01); P for interaction = 0.06

Cox model was stratified by sex, age and centre, and additionally adjusted for smoking status, education level, body mass index (kg/m²), 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