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.

Raul Zamora-Ros[1,*], Muath A. Alghamdi[1,2], Valerie Cayssials[1], Silvia Franceschi[3], Martin Almquist[4,5], Joakim Hennings[6], Maria Sandström[7], Konstantinos K. Tsilidis[8,9], Elisabete Weiderpass[10,11,12,13], Marie-Christine Boutron-Ruault[14,15], Bodil Hammer Bech[16], Kim Overvad[16], Anne Tjønneland[17], Kristina E.N. Petersen[17], Francesca Romana Mancini[14,15], Yahya Mahamat-Saleh[14,15], Fabrice Bonnet[14,15,18], Tilman Kühn[19], Renée T. Fortner[19], Heiner Boeing[20], Antonia Trichopoulou[21,22], Christina Bamia[21,22], Georgia Martimianaki[21], Giovanna Masala[23], Sara Grioni[24], Salvatore Panico[25], Rosario Tumino[26], Francesca Fasanelli[27], Guri Skeie[10], Tonje Braaten[10], Cristina Lasheras[28], Elena Salamanca-Fernández[29,30], Pilar Amiano[30,31], Maria-Dolores Chirlaque[30,32,33], Aurelio Barricarte[30,34,35], Jonas Manjer[4], Peter Wallström[36], H. Bas Bueno-de-Mesquita[9,37,38,39], Petra H Peeters[40], Kay-Thee Khaw[41], Nicholas J. Wareham[42], Julie A. Schmidt[43], Dagfinn Aune[9], Graham Byrnes[44], Augustin Scalbert[44], Antonio Agudo[1], Sabina Rinaldi[44]

Author affiliations

[1]Unit of Nutrition and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain.

[2]College of Medicine, Al Imam Mohammed Ibn Saud Islamic University, Riyadh, Saudi Arabia.

[3]Epidemiology Unit, Aviano Cancer Center, Milan, Italy.

[4]Department of Surgery, Skåne University Hospital Malmö, Lund University, Lund, Sweden

[5]Malmö Diet and Cancer Study, University Hospital Malmö, Malmö, Sweden

[6]Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden

[7]Department for Radiation Sciences, Umeå University, Umeå, Sweden

[8]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

[9]School of Public Health, Imperial College London, London, UK

[10]Department of Community Medicine, Faculty of Health Sciences, UiT, The Artic University of Tromsø, Tromsø, Norway.

[11]Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway.

[12]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

[13]Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland.

[14]CESP, Université Paris-Sud, UVSQ, INSERM, Université Paris-Saclay, Villejuif, France.

[15]Institut Gustave Roussy, Villejuif, France.

[16]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark.

[17]Unit of Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark.

[18]CHU Rennes, Université de Rennes 1, Rennes, France

[19]Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany.

[20]Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.

[21]Hellenic Health Foundation, Athens, Greece

[22]WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Dept. of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Greece

[23]Cancer Risk Factors and Life-Style Epidemiology Unit, Cancer Research and Prevention Institute – ISPO, Florence, Italy

[24]Nutritional Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

[25]Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy.

[26]Cancer Registry and Histopathology Unit, "Civic M.P. Arezzo" Hospital, ASP Ragusa, Italy.

[27]Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and University of Turin, Turin, Italy.

[28]Department of Functional Biology. Faculty of Medicine. University of Oviedo. Asturias, Spain

[29]Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.Granada. Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain.

[30]CIBER de Epidemiología y Salud Pública (CIBERESP), Spain.

[31]Public Health Division of Gipuzkoa, Regional Government of the Basque Country, Spain

[32]Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[33]Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain

[34]Navarra Public Health Institute, Pamplona, Spain

[35]Navarra Institute for Health Research (IdiSNA) Pamplona, Spain

[36]Nutrition Epidemiology Research Group, Department of Clinical Sciences, Lund University, Malmö, Sweden

[37]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[38]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands.

[39]Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

[40]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[41]Department of Public Health and Primary Care, University of Cambridge, UK

[42]MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK

[43]Cancer Epidemiology Unit, University of Oxford, UK

[44]International Agency for Research on Cancer (IARC), Lyon, France.

The entire manuscript is 3064 words (including abstract (202 words), text (2,862 words), 27 references, 2 tables, 2 supplementary table).

Running Title: Coffee and tea and thyroid cancer in EPIC

Corresponding author: Raul Zamora-Ros, Unit of Nutrition and Cancer, Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), Av Gran Via 199-203, 08908 L'Hospitalet de Llobregat, Spain. Phone: +34 932067401. Fax: +34 932607787. E-mail: rzamora@idibell.cat

ORCID numbers: Raul Zamora-Ros (0000-0002-6236-6804); Valerie Cayssials (0000-0003-4155-298X); Elisabete Weiderpass (0000-0003-2237-0128); Augustin Scalbert (0000-0001-6651-6710); Antonio Agudo (0000-0001-9900-5677)

Author list for Indexing: Zamora-Ros R, Alghamdi MA, Cayssials V, Franceschi S, Almquist M, Hennings J, Sandström M, Tsilidis KK, Weiderpass E, Boutron-Ruault M-C, 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 M-D, Barricarte A, Manjer J, Wallström P, Bueno-de-Mesquita HB, Peeters PH, Khaw K-T, Wareham NJ, Schmidt JA, Aune D, Byrnes G, Scalbert A, Agudo A, Rinaldi S.

Key words: Thyroid cancer, coffee, tea, Intake, cohort, EPIC

Abbreviations: 24-HDR: 24-h dietary recall; BMI: Body Mass Index; CI: Confidence Interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: Hazard Ratio; IARC: International Agency for Research on Cancer; NOS: Not Otherwise Specified; TC: Thyroid cancer

Acknowledgements: We thank Mr Bertrand Hémon for his valuable help with the EPIC database. The authors also thank all participants in the EPIC cohorts for their invaluable contribution to the study.

Financial support: 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) (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); 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) (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). RZ-R would like to

thank the “Miguel Servet” program (CP15/00100) from the Institute of Health Carlos III (Spain) and the European Social Fund (ESF).

Conflict of interest and Funding disclosure: Zamora-Ros R, Alghamdi MA, Cayssials V, Franceschi S, Almquist M, Hennings J, Sandström M, Tsilidis KK, Weiderpass E, Boutron-Ruault M-C, 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 M-D, Barricarte A, Manjer J, Wallström P, Bueno-de-Mesquita HB, Peeters PH, Khaw K-T, Wareham NJ, Schmidt JA, Aune D, Byrnes G, Scalbert A, Agudo A, Rinaldi S have no conflict of interest.

ABSTRACT

Purpose: Coffee and tea constituents have shown several anti-carcinogenic activities in cellular and animal studies, including against thyroid cancer (TC). However, epidemiological evidence is still limited and inconsistent. Therefore, we aimed to investigate this association in a large prospective study.

Methods: The study was conducted in the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort, which included 476,108 adult men and women. Coffee and tea intakes were assessed through validated country-specific dietary questionnaires.

Results: During a mean follow-up of 14 years, 748 first incident differentiated TC cases (including 601 papillary and 109 follicular TC) were identified. Coffee consumption (per 100mL/day) was not associated either with total differentiated TC risk ($HR_{calibrated}$=1.00, 95% CI 0.97-1.04) or with the risk of TC subtypes. Tea consumption (per 100mL/day) was not associated with the risk of total differentiated TC ($HR_{calibrated}$=0.98, 95% CI 0.95-1.02) and papillary tumor ($HR_{calibrated}$=0.99, 95% CI 0.95-1.03); whereas an inverse association was found with follicular tumor risk ($HR_{calibrated}$=0.90, 95% CI 0.81-0.99), but this association was based on a sub-analysis with a small number of cancer cases.

Conclusions: In this large prospective study, coffee and tea consumptions were not associated with TC risk. .

INTRODUCTION

Thyroid cancer (TC) is considered the most common endocrine cancer, and its incidence has been continuously increasing in the last decades [1], especially due to over-diagnosis [2]. In Europe, the number of new TC cases in 2012 was 53,000 and it is usually 3-fold more common in women than in men [3]. Differentiated TC, including papillary and follicular carcinoma, represents 90% of TC [4]. Only few risk factors have been well-established for TC, such as history of having a benign thyroid tumor, exposure to ionizing radiation in childhood, and body fatness [4,5]. Dietary factors, such as nutrients and components (e.g., energy, polyunsaturated fatty acids, alcohol, and flavonoids) [6-8] and foods (e.g., fish, fruits and vegetables, coffee and tea) [9-12], have been suggested to play a role in TC etiology, although until now epidemiological evidence is still very limited and inconclusive [4].

After water, coffee and tea are the most consumed beverages worldwide in adults [13]. Tea and coffee are rich sources of flavonoids and phenolic acids, respectively [14]. Basic research has shown that these polyphenol classes may play a role in cancer prevention, including TC [15], through the modulation of enzyme activities and signal transduction pathways related to cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis and metastasis [16,17]. However, other coffee and tea constituents, such as caffeine and theophylline, have shown both negative and positive effects in carcinogenesis [18]. Epidemiological evidence on the association between coffee and tea intake and TC risk is limited; a protective association on tea consumption and TC risk was observed in a recent meta-analysis [11], while no association was found with coffee intake in another meta-analysis [12]. Those results need to be interpreted with caution because of potential biases, since most of the studies published so far were case-control studies and included a small number of TC cases. Therefore, further large cohort studies are warranted.

In the current study, we aimed to investigate the relationships between coffee and tea consumption, and the risk of differentiated TC within the European Prospective Investigation into Cancer and Nutrition (EPIC), a large cohort with a relatively high number of TC cases and a wide variability in the intake of these beverages.

MATERIAL AND METHODS

Study population

EPIC is an ongoing multi-center cohort study aimed to evaluate the associations between dietary, lifestyle and genetic factors and cancer risk. The study enrolled 521,324 subjects (70.1% women) between 1992 and 2000, mostly aged between 35-70 years, from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom). The participants were mostly chosen from the general population with some exceptions. Further details of the study have been previously described [19]. The study was performed in accordance with the Declaration of Helsinki. Moreover, the ethical approval was provided from the review boards of the International Agency for Research on Cancer and local participating centers. Written informed consent was also provided by all study participants. Exclusions before the beginning of the analyses included: participants with missing or null follow-up time or having a prevalent cancer other than non-melanoma skin cancer at baseline (n =29,332); participants with incomplete information on lifestyle (n =1,277); and participants with dietary data unavailable or considered to be implausible (i.e. participants in the highest and lowest 1% of the distribution for the ratio between energy intake to estimated energy requirement, n= 14,555). Therefore, our analysis included 476,108 participants (333,876 women and 142,232 men).

Dietary and lifestyle assessment

At enrollment, dietary information over the previous 12 months was collected using country/center specific dietary questionnaires [19]. The relative validity and reproducibility of these questionnaires has been previously published [20]. In all countries, dietary questionnaires were self-reported, except in in Ragusa and Naples (Italy), Greece and Spain, where they were administered by trained interviewers. In Norway, data on tea consumption were not collected. Data on consumption of coffee type, i.e. caffeinated and decaffeinated, were only specified in some centers [France, Germany, Greece, Italy (Florence, Varese and Turin only), the Netherlands and the United Kingdom]. A standardized computerized 24-h dietary recall was used to obtain a second dietary measurement (between 1995 and 1999) from a random sample of the cohort (n=36,994) to calibrate dietary measurements across countries and to correct for systematic over- or under-estimation of dietary intakes [21]. The quantity of coffee and tea intake was converted from cups per month, week or day in the dietary questionnaires into mL/day using the typical sizes of tea/coffee cups for each center.

Lifestyle questionnaires were used to obtain information on education (used as a proxy for socioeconomic status), smoking status and intensity, alcohol consumption, physical activity levels [22], oral contraceptive use, menopausal status, and menopausal hormone use. Anthropometry (weight and height) was measured at recruitment by trained personnel, with the exception of Oxford (United Kingdom), Norway, and France, where measurements were self-reported [19].

Follow-up and case ascertainment

Incident cancer cases were identified through population cancer registries in all countries except France, Germany and Greece where cases were identified through active follow-up, directly from the participants or next of kin, and confirmed by a combination of methods, such as health insurance records, and cancer and pathology registries. Mortality data were

obtained from mortality registries at the regional or national level. Complete follow-up censoring dates ranged from December 2010 to December 2014, depending on the study centre.

The 10th Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-10) was used to code TC (code C73). In this analysis only differentiated TC cases were included, and therefore, of the 800 TC cases ascertained, anaplastic (n=9), medullary (n=37), lymphoma (n=1) forms, and "other morphologies" (n=5) of TC cases were excluded. Finally, 748 first primary incident differentiated TC cases were considered: 601 papillary TCs, 109 follicular TCs, and 38 not otherwise specified (NOS) TCs, most likely to be papillary TCs.

Statistical analysis

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) between coffee and tea consumption and differentiated TC risk. Intakes of coffee and tea were analyzed as continuous variables (increments of 100 mL/day). Coffee consumers were also analyzed using cohort-wide quartiles. Due to the high percentage of tea non-consumers (33.9%), individual tea consumption was classified as non-consumers, and cohort-wide tertiles established among consumers. Tests for linear trend were performed by attributing the median of each category as score. Age was the primary time variable in all models. Entry time was age at recruitment and exit time was age at first diagnosis of any type of cancer, death, or censoring date (loss or end of follow-up), whichever occurred first. Tests and graphs based on Schoenfeld residuals were used to assess proportional hazards assumptions, which were satisfied. The basic model (model 1) was stratified by sex, age at recruitment (1-year interval) and center. The multivariable model (model 2) was additionally adjusted for body mass index (BMI, continuous variable in kg/m^2), smoking status (never, former, current smoker and unknown), alcohol consumption (g/day), education level

(primary, secondary and unknown), physical activity (inactive, active and unknown according to the Cambridge Physical Activity Index) [22], and total energy intake (kcal/day). In women, model 2 was also adjusted for menopausal status and type (pre-, peri-, post-, and surgical menopause), ever use of oral contraceptives (yes, no and unknown), and history of infertility problems (yes, no and unknown).

Separate analyses were performed for differentiated TC subtypes: follicular and papillary tumors. Heterogeneity of risk between TC subtypes was assessed with the Wald test [23]. Possible interactions of coffee/tea consumption with sex, body mass index (categorical variable: BMI<25 and BMI≥25), tobacco smoking status (never, former, and current smokers), and physical activity (inactive and active) were tested by including an interaction term in the multi-adjusted models. Separate BMI-specific models were fitted because a significant interaction between BMI categories (BMI<25 and BMI≥25) and coffee intake was detected. Sensitivity analyses were performed by repeating the models after the exclusion of differentiated TC cases diagnosed during the first 2 years of follow-up, since participants may have changed their diets in the pre-diagnostic period. Finally, we also conducted analyses using country-specific levels of coffee consumption instead of overall cohort-wide levels of consumption, because coffee volumes and compositions notably differed among EPIC countries. For all analyses, p-values <0.05 were considered as statistically significant. Statistical analyses were conducted by using SAS, version 9.3, software (SAS Institute).

Calibration of dietary data

A calibration method was used to correct for between-center errors and to correct for random and systematic within-person errors. In this method, the 24-HDR values of 36,994 participants were regressed on the main dietary questionnaire values for coffee and tea with adjustment for age at recruitment, center, and total energy intake, and weighting by day of the week and season of the year during which the 24-HDR was collected [24]. Zero consumption

values in the main dietary questionnaires were excluded in the regression calibration models, and a zero was directly imputed as a corrected value. Country and sex-specific calibration models were used to obtain individual predicted values of dietary exposure for all participants. Cox regression models were then run using the predicted (calibrated) values for each individual on a continuous scale and those results are considered as the main exposure in this study. The standard error of the calibrated coefficient was estimated with bootstrap sampling in the calibration and disease models and repeated 300 times [24].

RESULTS

Overall, 748 subjects (666 women and 82 men) out of 467,108 participants (333,876 women and 142,232 men) were diagnosed with a first primary incident differentiated TC during the follow-up. The median (percentile 10 and 90%) of coffee consumption was 357 (16-1,000) mL/day and 289 (4-857) mL/day in men and women, respectively; the highest intake was in Denmark and the lowest ones in Italy and Spain. The median (percentile 10 and 90%) of tea consumption was 12 (0-625) mL/day and 14 (0-645) mL/day in men and in women, respectively. The highest consumption of tea in both men and women was in the UK, whereas the lowest consumption of tea in men and women was in Spain, Greece and Sweden (median ≤ 1 mL/day) (**Table1**).

Participants in the highest quartile of coffee consumption were more likely to be men, current smokers, physically active, highly educated, and to have higher intakes of alcohol and total energy than those in the lowest quartile. Tea consumers in the highest consumption group were more likely to be women, more physically active, highly educated, had lower BMI and waist circumference and consumed less alcohol, tobacco and total energy than non-tea consumers (**Supplementary table 1**).

No association was observed between calibrated coffee consumption per 100mL/d and the risk of total differentiated TC ($HR_{calibrated}$ = 1.00, 95% CI 0.97-1.04), papillary tumor

($HR_{calibrated}$ = 1.00, 95% CI 0.96-1.04) and follicular tumor ($HR_{calibrated}$ = 1.05, 95% CI 0.96-1.14), (P for heterogeneity =0.29) (**Table 2**). Similarly, null results were found between coffee intake, using both cohort-wide (Table 2) and country-specific quartiles (data not shown), and differentiated TC risk. Similar null results were observed after excluding 77 cases who were diagnosed with differentiated TC within the first 2 years of follow-up.

No significant association was found between calibrated tea intake per 100mL/d and the risk of total differentiated TC ($HR_{calibrated}$ = 0.98, 95% CI 0.95-1.02). A borderline statistically significant heterogeneity was observed between TC site risks for tea intake (P for heterogeneity =0.055). No statistically association with papillary tumor ($HR_{calibrated}$ = 0.99, 95% CI 0.95-1.03) was found, whereas an inverse association was observed with follicular tumor risk ($HR_{calibrated}$ = 0.90, 95% CI 0.81-0.99). In the sensitivity analysis after excluding 77 cases who were diagnosed with differentiated TC within the first 2 years of follow-up, the results were almost identical, including the association between calibrated tea intake (per 100mL/d) and follicular tumor risk ($HR_{calibrated}$ = 0.89, 95% CI 0.79-1.00) (data not tabulated).

The risk estimates for coffee consumption and differentiated TC were modified by BMI categories (BMI<25 and BMI≥25), with a positive association in subjects below BMI 25, and inverse associations in subjects with BMI 25 and above (p for interaction=0.009). However, no individual association was statistically significant in either stratum. (**Supplementary table 2**). No interactions were detected by sex (p=0.72 and 0.76, respectively), tobacco (p=0.87 and 0.48, respectively), and physical activity (p=0.34 and 0.43, respectively).

DISCUSSION

In this large prospective study, we observed no association between both coffee or tea consumption and overall differentiated TC risk in either men or women, or for either papillary or follicular tumors.

Similarly to our findings, in a recent meta-analysis of 7 epidemiological studies, including only 2 prospective cohorts (including 109 and 159 TC cases), no association between coffee intake and TC risk was found [12]. Authors of the meta-analysis recommended further prospective studies on this topic evaluating potential differences between sexes, histological subtypes and coffee types, and estimating dose-response relationships. We were able to investigate most of these issues, since the number of TC cases in our cohort was more than 4-fold larger than the previous prospective studies [25,26]. Our study shows null results in both men and women, as well as in either papillary or follicular tumors. Indeed, the results were not statistically significant using either quartiles or the continuous variable. The collection of data on caffeinated and decaffeinated coffee was limited to a few EPIC centers, which hampers statistical power for these analyses and therefore our ability to draw any conclusions on possible associations. To our knowledge, only one population-based case-control study reported separate association estimates for caffeinated and decaffeinated coffee with TC, showing null results for both associations [27]. Moreover, in Europe, coffee brewing methods vary greatly among countries, with Northern populations drinking large quantities of diluted coffee, and Southern populations principally consuming concentrated coffee, such as espressos. Despite the fact that we did not collect data on brewing method, which could have varied by country, no association between coffee and TC risk was observed using country-specific quartiles.

In the present study, no association was found between tea consumption, which in Europe is mostly black tea, and overall differentiated TC risk. In 2015, a meta-analysis of 11 studies, including only one cohort study (including 159 TC cases), showed an inverse association between tea intake and overall TC risk for the highest versus the lowest category of tea consumption (risk estimate = 0.77, 95% CI 0.62-0.97) [11]. This association was, however, only detected in the case-control studies, that are more prone to recall bias. In the subgroup

analysis by geographic locations, the association was statistically significant only in the US-based studies; however, it was not confirmed in a recent US cohort: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) prospective study [25]. Regarding histological subtypes, no association was observed with papillary TC risk in our study; whereas an inverse association was detected with follicular TC risk (using the continuous variable but not the categorical one). Cellular and animal experiments have shown protective effects of tea constituents, particularly flavonoids, against TC [15]. Despite the biological plausibility of an inverse association between tea consumption and TC risk and the potential etiological differences between papillary and follicular TC, it is important to bear in mind that in our study the number of follicular cancer cases is rather low (n=109) and this may be the result of multiple comparisons and sub-set analyses. Therefore, the results were probably due to chance. Unfortunately, there was no data on the relationship by histological subtypes in the meta-analysis [11]. Hence, further prospective studies are warranted to evaluate this relationship between tea consumption and follicular TC risk.

Major strengths of our study were its prospective design, the long follow-up, and its large sample size with a relatively high number of TC cases. However, our study had some limitations. Firstly, our results may be influenced by measurement errors in the dietary assessment that may have attenuated our findings; although we partially controlled them using validated country-specific dietary questionnaire [20] and calibrating the associations using the 24-HDR [24]. Secondly, diet was only assessed at baseline, and that any potential dietary changes during follow-up are unaccounted for. In addition, coffee data on brewing method was not collected; although differences in brewing methods are larger in participants from different countries than in participants in the same country. Results were almost identical using either cohort-wide or country-specific quartiles of coffee consumption. Moreover, limited data on coffee type (caffeinated or decaffeinated coffee) and no data on tea type

(green, black, white or oolong tea) was available in this study. In addition, some individuals may have modified their diet during the early prediagnostic period of the disease, but sensitivity analyses excluding incident cases diagnosed in the first 2 years of follow-up did not alter the risk estimates. Finally, we have adjusted our models for several potential confounders, although the presence of possible residual confounding cannot be excluded.

In conclusion, no association between coffee and tea consumption and the risk of overall differentiated TC was found in this large multi-center European cohort. Null results were also observed between coffee intake and both papillary and follicular TC risk. For tea consumption, our study shows no association and an inverse association with papillary and follicular TC risk, respectively, but these sub-analyses' findings should be interpreted with caution. Future studies capturing coffee brewing methods, using nutritional biomarkers [26] and repeated measurements of coffee and tea intake during the follow-up might further develop our understanding of the association between tea and coffee consumption and TC risk.

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.

AUTHORS' CONTRIBUTIONS:

RZ-R, SF and SR designed the research; RZ-R, MAA and VC performed the statistical analyses; RZ-R and MAA drafted the manuscript; SF, MA, JH, MS, KKT, EW, M-CB-R, GB, AS, AA, SR contributed to the discussion. All authors reviewed, edited and approved the final manuscript.

REFERENCES

1. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R (2013) Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013:965212. https://doi.org/10.1155/2013/965212

2. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L (2016) Worldwide Thyroid-Cancer Epidemic? The Increasing Impact of Overdiagnosis. N Engl J Med 375:614-617. https://doi.org/10.1056/NEJMp1604412

3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-E386. https://doi.org/10.1002/ijc.29210

4. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S (2009) Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. Cancer Causes Control 20:75-86. https://doi.org/10.1007/s10552-008-9219-5

5. 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 (2016) Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective Studies. Thyroid 26:306-318. https://doi.org/10.1089/thy.2015.0319.

6. 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 (2015) Baseline and lifetime alcohol consumption and risk of differentiated thyroid carcinoma in the EPIC study. Br J Cancer 113:840-847. https://doi.org/10.1038/bjc.2017.235.

7. 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 (2016) Energy and macronutrient intake and risk of differentiated thyroid carcinoma in the European Prospective Investigation into Cancer and Nutrition study. Int J Cancer 138:65-73. https://doi.org/10.1002/ijc.29693

8. Xiao Q, Park Y, Hollenbeck AR, Kitahara CM (2014) Dietary flavonoid intake and thyroid cancer risk in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 23:1102-1108. https://doi.org/10.1158/1055-9965.EPI-13-1150

9. 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 (2018) 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 142:449-459. https://doi.org/10.1002/ijc.30880.

10. Zamora-Ros R, Castaneda J, Rinaldi S, Cayssials V, Slimani N, Weiderpass E, Tsilidis KK, Boutron-Ruault MC, Overvad K, Eriksen AK, Tjønneland A, Kühn T, Katzke V, Boeing H, Trichopoulou A, La Vecchia C, Kotanidou A, Palli D, Grioni S, Mattiello A, Tumino R, Sciannameo V, Lund E, Merino S, Salamanca-Fernández E, Amiano P, Huerta JM, Barricarte A, Ericson U, Almquist M, Hennings J, Sandström M, Bueno-de-Mesquita HB, Peeters PH, Khaw KT, Wareham NJ, Schmidt JA, Cross AJ, Riboli E, Scalbert A, Romieu I, Agudo A, Franceschi S (2017) Consumption of Fish Is Not Associated with Risk of Differentiated Thyroid Carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. J Nutr 147:1366-1373. https://doi.org/10.3945/jn.117.247874

11. Ma S, Wang C, Bai J, Wang X, Li C (2015) Association of tea consumption and the risk of thyroid cancer: a meta-analysis. Int J Clin Exp Med 8:14345-14351.

12. Han MA, Kim JH (2017) Coffee Consumption and the Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 14.pii:E129. https://doi.org/10.3390/ijerph14020129

13. Di Lorenzo A, Curti V, Tenore GC, Nabavi SM, Daglia M (2017) Effects of Tea and Coffee Consumption on Cardiovascular Diseases and Relative Risk Factors: An Update. Curr Pharm Des 23:2474-2487. https://doi.org/10.2174/1381612823666170215145855.

14. 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, Peppa 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 (2016) Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nutr 55:1359-1375. https://doi.org/10.1007/s00394-015-0950-x

15. Gonçalves CFL, de Freitas ML, Ferreira ACF (2017) Flavonoids, Thyroid Iodide Uptake and Thyroid Cancer-A Review. Int J Mol Sci 18: E1247. https://doi.org/10.3390/ijms18061247.

16. Clere N, Faure S, Martinez MC, Andriantsitohaina R (2011) Anticancer properties of flavonoids: roles in various stages of carcinogenesis. Cardiovasc Hematol Agents Med Chem 9:62-77.

17. Ramos S (2008) Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. Mol Nutr Food Res 52:507-526. https://doi.org/10.1002/mnfr.200700326.

18. Sabisz M, Skladanowski A. Modulation of cellular response to anticancer treatment by caffeine: inhibition of cell cycle checkpoints, DNA repair and more. Curr Pharm Biotechnol 2008;9:325-336.

19. 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, Thiébaut 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 (2002) European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 5:1113-1124.

20. Margetts BM, Pietinen P (1997) European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. Int J Epidemiol 26 Suppl 1:S1-S5.

21. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, Bellegotti M, Ocké MC, Peeters PH, Engeset D, Lund E, Agudo A, Larrañaga N, Mattisson I, Andren C, Johansson I, Davey G, Welch AA, Overvad K, Tjønneland A, Van Staveren WA, Saracci R, Riboli

E (2002) European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr 5:1125-1145.

22. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE (2003) 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 6:407-413.

23. Wang M, Spiegelman D, Kuchiba A, Lochhead P, Kim S, Chan AT, Poole EM, Tamimi R, Tworoger SS, Giovannucci E, Rosner B, Ogino S (2016) Statistical methods for studying disease subtype heterogeneity. Stat Med 35(5):782-800. https://doi.org/10.1002/sim.6793.

24. Ferrari P, Kaaks R, Fahey MT, Slimani N, Day NE, Pera G, Boshuizen HC, Roddam A, Boeing H, Nagel G, Thiebaut A, Orfanos P, Krogh V, Braaten T, Riboli E; European Prospective Investigation into Cancer and Nutrition study (2004) Within- and between-cohort variation in measured macronutrient intakes, taking account of measurement errors, in the European Prospective Investigation into Cancer and Nutrition study. Am J Epidemiol 160:814-822.

25. Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, La Vecchia C (2015) Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. Br J Cancer 113:809-816. https://doi.org/10.1038/bjc.2015.276.

26. Michikawa T, Inoue M, Shimazu T, Sasazuki S, Iwasaki M, Sawada N, Yamaji T, Tsugane S (2011) Green tea and coffee consumption and its association with thyroid cancer risk: a population-based cohort study in Japan. Cancer Causes Control 22:985-993. https://doi.org/10.1007/s10552-011-9771-2

27. Frentzel-Beyme R, Helmert U (2000) Association between malignant tumors of the thyroid gland and exposure to environmental protective and risk factors. Rev Environ Health 15:337-358.

28. Edmands WM, Ferrari P, Rothwell JA, Rinaldi S, Slimani N, Barupal DK, Biessy C, Jenab M, Clavel-Chapelon F, Fagherazzi G, Boutron-Ruault MC, Katzke VA, Kühn T, Boeing H, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Grioni S, Tumino R, Vineis P, Mattiello A, Romieu I, Scalbert A (2015) Polyphenol metabolome in human urine and its association with intake of polyphenol-rich foods across European countries. Am J Clin Nutr 102:905-913. https://doi.org/ 10.3945/ajcn.114.101881

Table 1. Number of differentiated TC cases and median (10th-90th percentile) of coffee and tea intake by sex and country in the EPIC study.

	Women							Men						
		Cancer cases							Cancer cases					
Country	N	TC	Papillary	Follicular	NOS	Coffee (mL/d)	Tea (mL/d)	N	TC	Papillary	Follicular	NOS	Coffee (mL/d)	Tea (mL/d)
France	67,391	248	227	19	2	225 (0-616)	26 (0-564)	-	-	-	-	-	-	-
Italy	30,511	106	81	16	9	90 (0-184)	5 (0-150)	14,032	21	16	3	2	90 (30-180)	3 (0-150)
Spain	24,846	74	62	11	1	100 (0-300)	0 (0-0)	15,138	6	4	2	0	75 (0-232)	0 (0-0)
United Kingdom	52,565	39	24	10	5	217 (4-857)	475 (2-1140)	22,850	5	5	0	0	475 (4-857)	475 (2-1140)
The Netherlands	26,910	13	10	3	0	500 (125-875)	238 (4-619)	9,627	4	2	1	1	625 (125-1125)	119 (0-475)
Greece	15,229	28	22	1	5	140 (5-340)	0 (0-11)	10,815	8	6	0	2	170 (33-420)	0 (0-11)
Germany	27,373	67	47	18	2	342 (52-784)	24 (0-401)	21,178	15	11	3	1	392 (41-900)	21 (0-398)
Sweden	26,365	29	20	4	5	385 (107-750)	0 (0-250)	22,301	10	5	3	2	400 (108-829)	1 (0-250)
Denmark	28,714	26	18	8	0	900 (86-1300)	157 (0-900)	26,291	13	10	3	0	900 (200-1600)	29 (0-900)
Norway	33,972	36	31	4	1	360 (60-780)	-	-	-	-	-	-	-	-
TOTAL	**333,876**	**666**	**542**	**94**	**30**	**289 (4-857)**	**14 (0-645)**	**142,232**	**82**	**59**	**15**	**8**	**357 (16-1000)**	**12 (0-625)**

Abbreviations: TC thyroid cancer, NOS not otherwise specified

Table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for differentiated thyroid cancer (TC), and subtypes, according to quartile of intake of coffee and tea in the EPIC study.

	Differentiated TC			Papillary tumour			Follicular tumour			
	N of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	N of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	N of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	P for heterogeneity
Coffee										
Quartile 1	241	1.00 (ref)	1.00 (ref)	197	1.00 (ref)	1.00 (ref)	31	1.00 (ref)	1.00 (ref)	
Quartile 2	209	0.85 (0.70-1.03)	0.86 (0.71-1.04)	173	0.87 (0.70-1.07)	0.87 (0.71-1.08)	24	0.74 (0.43-1.28)	0.74 (0.43-1.28)	
Quartile 3	158	0.92 (0.74-1.16)	0.93 (0.75-1.17)	126	0.90 (0.70-1.15)	0.90 (0.70-1.16)	24	1.12 (0.60-2.08)	1.15 (0.62-2.14)	
Quartile 4	140	1.01 (0.80-1.29)	1.01 (0.79-1.29)	105	0.95 (0.73-1.25)	0.95 (0.72-1.26)	30	1.51 (0.81-2.81)	1.48 (0.78-2.80)	
P-trend		0.69	0.72		0.85	0.85		0.09	0.11	
Observed continuous (per 100mL/d)		1.01 (0.99-1.04)	1.01 (0.99-1.04)		1.01 (0.98-1.04)	1.01 (0.98-1.04)		1.06 (0.99-1.12)	1.05 (0.99-1.12)	0.21
Calibrated continuous (per 100mL/d)		1.01 (0.97-1.04)	1.00 (0.97-1.04)		1.00 (0.96-1.04)	1.00 (0.96-1.04)		1.05 (0.97-1.14)	1.05 (0.96-1.14)	0.29
Tea[1]										
Group 1	278	1.00 (ref)	1.00 (ref)	219	1.00 (ref)	1.00 (ref)	45	1.00 (ref)	1.00 (ref)	
Group 2	154	1.11 (0.88-1.38)	1.12 (0.89-1.40)	117	1.11 (0.86-1.43)	1.12 (0.87-1.44)	25	0.82 (0.47-1.44)	0.85 (0.48-1.48)	
Group 3	193	1.18 (0.96-1.45)	1.20 (0.97-1.47)	165	1.29 (1.03-1.62)	1.30 (1.04-1.64)	21	0.58 (0.33-1.03)	0.60 (0.34-1.08)	
Group 4	87	0.91 (0.68-1.22)	0.93 (0.70-1.25)	69	1.00 (0.73-1.37)	1.01 (0.73-1.39)	14	0.50 (0.23-1.06)	0.52 (0.24-1.13)	
P-trend		0.39	0.46		0.88	0.92		0.12	0.10	
Observed continuous (per 100mL/d)		0.98 (0.95-1.01)	0.98 (0.95-1.01)		0.99 (0.96-1.03)	0.99 (0.96-1.03)		0.90 (0.81-0.99)	0.90 (0.82-0.99)	0.029
Calibrated continuous (per 100mL/d)		0.98 (0.95-1.02)	0.98 (0.95-1.02)		0.99 (0.95-1.03)	0.99 (0.95-1.03)		0.90 (0.81-0.99)	0.90 (0.81-0.99)	0.055

[1]Tea was classified as group 1: non-consumers; group 2-4: tertiles of tea consumers

Model 1: stratified by center, age at baseline (1-year interval) and sex.

Model 2: additionally adjusted for body mass index, smoking status, education level, physical activity, total energy and alcohol intake. In women, also adjusted for menopause status and type, oral contraceptive use, and infertility problems.

Supplementary table 1. Baseline characteristics by quartile of coffee and tea consumption in the EPIC study.

	Coffee				Tea[3]			
	Q1 (n=118,982)	Q2 (n=117,671)	Q3 (n=119,423)	Q4 (n=120,032)	G1 (n=149,783)	G2 (n=94,184)	G3 (n=100,694)	G4 (n=97,475)
Cutoffs (mg/d)	<94	94-299	300-540	>540	0	>0-42	43-428	>428
Sex, women (%)	72.7	71.3	71.6	64.9	66.5	61.4	72.7	71.1
Country (%)								
France	16.1	17.9	14.5	8.2	18.4	9.2	20.9	10.4
Italy	20.6	16.5	0.5	<0.1	13.4	12.9	11.9	0.4
Spain	16.9	14.0	2.4	0.4	25.6	0.3	1.2	0.1
UK	18.9	12.9	17.8	13.8	1.4	11.8	10.0	53.5
The Netherlands	2.7	4.4	10.0	13.5	2.6	5.3	18.9	9.0
Greece	7.5	10.4	3.4	0.7	8.0	13.7	1.1	<0.1
Germany	5.2	11.8	12.0	11.8	7.8	18.3	14.8	4.9
Sweden	3.3	6.4	17.4	13.7	17.0	11.7	9.6	2.5
Denmark	4.7	3.2	12.5	25.6	5.9	16.8	11.6	19.1
Norway	4.1	2.4	9.6	12.3				
Age (y)	50.6 (10.8)	51.3 (10.1)	51.6 (9.9)	51.4 (8.8)	52.7 (8.8)	50.0 (10.4)	50.4 (10.0)	52.0 (11.8)
Body mass index (kg/m^2)	25.5 (4.6)	25.6 (4.4)	25.1 (4.1)	25.5 (4.1)	26.3 (4.5)	25.7 (4.3)	24.9 (4.1)	24.7 (3.9)
Waist circumference (cm)	85.2 (13.3)	85.5 (13.0)	84.2 (12.7)	86.0 (12.9)	88.2 (13.0)	85.8 (13.2)	83.5 (12.5)	81.8 (12.2)
Total energy (kcal/d)	2052 (623)	2107 (624)	2025 (594)	2117 (631)	2149 (636)	2086 (642)	2101 (616)	2072 (575)
Alcohol (g/d)	10.5 (16.9)	12.3 (17.6)	11.8 (16.1)	13.3 (17.6)	13.6 (19.8)	12.9 (17.7)	12.1 (15.8)	11.5 (15.2)
Smoking status (%)[1]								
Never	60.2	52.7	48.7	34.4	49.1	47.7	52.1	51.8
Former	23.3	25.0	29.2	29.0	23.2	25.6	27.3	31.3
Current	14.5	20.3	19.7	35.0	26.1	25.0	18.9	14.8
Education level (%)[1]								

Primary	36.0	35.2	22.9	26.0	47.9	29.8	20.9	14.6
Secondary	56.7	61.4	73.3	71.4	50.9	67.7	76.5	75.1
Physical activity (%)[1]								
Inactive	61.0	59.5	50.0	45.3	63.8	54.9	49.8	52.1
Active	38.0	39.5	48.0	51.5	35.6	44.1	47.5	45.7
Menopause status (%)[1,2]								
Premenopausal	38.8	37.8	32.1	30.2	31.0	39.9	35.2	35.4
Perimenopausal	16.3	16.7	20.7	23.1	46.7	41.6	42.8	46.4
Postmenopausal	41.4	42.3	44.8	44.4	18.7	15.6	19.3	15.0
Surgical menopause	3.6	3.2	2.4	2.3	3.6	3.0	2.8	3.2
Oral contraceptive use (%)[1,2]								
No	48.4	45.6	36.7	33.8	52.6	41.7	34.8	34.1
Yes	51.7	54.4	63.3	66.2	47.4	58.3	65.2	65.9
Infertility problems (%)[1,2]								
No	94.9	95.4	95.6	95.7	95.2	95.6	95.4	95.2
Yes	5.1	4.6	4.4	4.3	4.8	4.4	4.6	4.8

Values are means and standard deviations.

[1]Missing values: smoking status 9,676 (2.03%), education level 16,929 (3.56%), physical activity 8,824 (1.85%), oral contraceptive use 8,427 (2.52%), infertility problems 111,162 (33.29%).

[2]Variables only available in women.

[3]Tea was classified as group 1: non-consumers; group 2-4: tertiles of tea consumers

Supplementary table 2. Hazard ratios (HR) and 95% confidence intervals (CI) for differentiated thyroid cancer (TC) stratified by body mass index (BMI) according to consumption of coffee and tea in the EPIC study.

	BMI<25			BMI≥25			
	N of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	N of cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	P for interaction
Coffee							
Quartile 1	115	1.00 (ref)	1.00 (ref)	126	1.00 (ref)	1.00 (ref)	
Quartile 2	99	0.88 (0.67-1.15)	0.88 (0.67-1.16)	110	0.80 (0.61-1.04)	0.80 (0.61-1.05)	
Quartile 3	101	1.16 (0.87-1.56)	1.17 (0.87-1.57)	57	0.64 (0.45-0.91)	0.64 (0.45-0.92)	
Quartile 4	81	1.27 (0.92-1.75)	1.25 (0.90-1.74)	59	0.70 (0.48-1.01)	0.70 (0.48-1.02)	
P-trend		0.058	0.074		0.058	0.066	0.009
Observed continuous (per 100mL/d)		1.04 (1.01-1.08)	1.04 (1.01-1.08)		0.97 (0.93-1.01)	0.97 (0.93-1.01)	
Calibrated continuous (per 100mL/d)		1.04 (0.99-1.09)	1.04 (0.99-1.09)		0.96 (0.91-1.01)	0.96 (0.91-1.01)	
Tea							
Quartile 1	132	1.00 (ref)	1.00 (ref)	146	1.00 (ref)	1.00 (ref)	
Quartile 2	72	0.96 (0.70-1.31)	0.96 (0.70-1.31)	82	1.29 (0.93-1.79)	1.30 (0.93-1.81)	
Quartile 3	114	1.04 (0.79-1.36)	1.04 (0.80-1.37)	79	1.42 (1.03-1.97)	1.44 (1.04-1.99)	
Quartile 4	55	0.84 (0.59-1.20)	0.85 (0.59-1.21)	32	1.04 (0.64-1.70)	1.06 (0.65-1.73)	
P-trend		0.37	0.40		0.93	0.96	0.63
Observed continuous (per 100mL/d)		0.99 (0.95-1.03)	0.99 (0.95-1.03)		0.97 (0.92-1.02)	0.97 (0.92-1.02)	
Calibrated continuous (per 100mL/d)		0.99 (0.95-1.04)	0.99 (0.95-1.04)		0.97 (0.91-1.03)	0.97 (0.91-1.03)	

Model 1: stratified by center, age at baseline (1-year interval) and sex.

Model 2: additionally adjusted for BMI, smoking status, education level, physical activity, total energy and alcohol intake. In women, also adjusted for menopause status and type, oral contraceptive use, and infertility problems.