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Consumption of fruits, vegetables, and fruit juices and differentiated thyroid carcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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Abstract

Fruit and vegetable (F&V) intake is considered as probably protective against overall cancer risk, but results in previous studies are not consistent for thyroid cancer (TC). The purpose of this study is to examine the association between the consumption of fruits, vegetables, fruit juices and differentiated thyroid cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The EPIC study is a cohort including over half a million participants, recruited between 1991 and 2000. During a mean follow-up of 14 years, 748 incident first primary differentiated TC cases were identified. F&V and fruit juice intakes were assessed through validated country-specific dietary questionnaires. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models adjusted for potential confounding factors. Comparing the highest vs. lowest quartile of intake, differentiated TC risk was not associated with intakes of total F&V (HR: 0.89; 95% CI: 0.68-1.15; p-trend=0.44), vegetables (HR: 0.89; 95% CI: 0.69-1.14; p-trend=0.56), or fruit (HR: 1.00; 95% CI: 0.79-1.26; p-trend=0.64). No significant association was observed with any individual type of vegetable or fruit. However, there was a positive borderline trend with fruit juice intake (HR: 1.23; 95% CI: 0.98-1.53; p-trend=0.06). This study did not find any significant association between F&V intakes and differentiated TC risk; however a positive trend with fruit juice intake was observed, possibly related to its high sugar content.

Keywords

Thyroid cancer; Fruits; Vegetables; Fruit juices; Intake; EPIC

Introduction

The consumption of fruits and vegetables (F&V) has been consistently associated with a reduced risk of many cancers in case-control studies, but these associations become weak or even null in cohorts.[1–3] In 2003 the World Health Organization (WHO)[4] and in 2007 the International Agency for Research on Cancer (IARC)[5] concluded that there was convincing evidence that F&V lower the risk of cardiovascular diseases and probable evidence for lower respiratory and digestive cancer risks. Therefore, they recommended an intake of 400–500 g/day, the well-known campaign of 5 a day (including vegetables, fruits and also juices, although juices are usually recommended ≤1 portion per day by several national nutrition health programmes, e.g. in the UK, France, Norway, etc.). However, little is known about its association with thyroid cancer (TC) risk, particularly in prospective studies. TC is the most common endocrine cancer (1-1.5% of all new cancers diagnosed each year) worldwide[6] and the incidence has been constantly increasing over the last three decades,[7–10] mainly explained by over-diagnosis.[11]

In 2014, a meta-analysis of 19 case-control studies on dietary factors and TC risk found a weak inverse association with the intake of vegetables and no association with the intake of fruits.[12] Cruciferous vegetables have been studied more closely due to their content in goitrogenic substances,[13] which have tumour promoting effects upon rats' thyroid.[14,15] Two recent meta-analyses of retrospective studies found either no association or a positive association between the intake of cruciferous vegetables and differentiated TC risk.[12,16] For juices, a positive association was suggested between citrus fruit juice intake and TC risk.[17]

The aim of the present study was to prospectively evaluate the association between the consumption of vegetables, fruits, fruit juices and their subtypes and differentiated TC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large cohort with a high heterogeneity in dietary intake across the participating countries.[18]

Material and Methods

Study population

EPIC is a multicentre prospective cohort study principally designed to investigate the relationships between diet and other environmental factors and cancer risk. The study design has been explained in detail previously.[19,20] In brief, EPIC enrolled more than half a million participants, 70% women, mostly aged between 35 and 70 years old from 23 centres in 10 western European countries (Denmark, France, Germany, Greece, Italy, Norway,

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Sweden, Spain, the Netherlands, and the United Kingdom) during the period 1991-2000. All participants gave their written informed consent, and the Internal Review Boards of the IARC and all ethical committees from participating centres approved the project.

Dietary assessment

Validated country-specific dietary questionnaires were used to evaluate participants' diets over the 12 months preceding recruitment.19 They were designed to collect the specificity of local dietary habits and provide optimal compliance. According to the centres, quantitative or semi-quantitative methods were applied. In Malmö-Sweden, a combination of a 7-day record and a semi-quantitative food frequency questionnaire was administered. Questionnaires were mainly self-reported except for Greece, Spain and two centres in Italy (Naples and Ragusa) where they were administered during a face-to-face interview. Lifestyle questionnaires about educational and socio-economic status, lifetime history of tobacco smoking and alcohol consumption, physical activity, menstrual and reproductive history and medical history were also collected at baseline.19

The analysed food groups were vegetables (potatoes and legumes were not included), fresh fruits (excluding nuts, olives, and seeds), and total juices or fruit juices (including citrus fruit juices, non-citrus fruit juices, vegetable juices and fruit nectars). Vegetable juices were rarely consumed (<2% of total juices) and this item was only recorded in the dietary questionnaires of 3 countries; for this reason we have simplified and used the term fruit juices instead of total juices. Total intake of F&V was calculated as the sum of fruits and vegetables, excluding fruit juices because of their large differences in nutritional composition compared to F&V.18 Subgroups of vegetables and fruits were also considered: leafy vegetables, fruiting vegetables, root vegetables, cabbages, mushrooms, grain and pod vegetables, onion/garlic, sprouts/stalk vegetables, citrus fruits, hard fruits (apples and pears), berries (strawberries, grapes, blueberries), stone fruits (peach, nectarine, apricot, plum, cherry), banana, and other fruits (fig, kiwi, melon, watermelon, pineapple). Details about the composition of the subgroups are given elsewhere.18

Follow-up and case ascertainment

Except for Germany and Greece, all information on vital status came from national or regional mortality registries. In Germany and Greece, those data were continuously collected through an active follow-up. Cancer incident cases were identified through regional/national cancer registries, except for German, Greek, and French centres. For those, different methods were used, including health insurance records, contacts with cancer pathology registries, and active follow-up through study participants or relatives. Complete follow-up censoring dates ranged from December 2010 to December 2014, depending on the study centre.19 Cancer cases were defined as subjects with a first primary TC (code C73 according to the International Classification of Diseases, 10th Revision) during follow-up. Differentiated TC comprises papillary and follicular tumours.

Of the 857 TC cases, anaplastic (n=9), medullary (n=37), lymphoma (n=1) forms and "other morphologies" (n=5) were excluded. Moreover, 29,332 participants (including 45 differentiated TC cases) were excluded from the initial database because of missing or null follow-time or having a prevalent cancer other than non-melanoma skin cancer. Further 1,277 and 14,555 participants (including 12 differentiated TC cases) were also excluded because their lifestyle and dietary data were not complete or coherent (they were in the top or the bottom 1% of the distribution of the total energy intake to energy requirement ratio), respectively. 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 papillary TCs. A total of 142,232 men and 333,876 women were included in the present study.

Statistical analysis

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Intakes of vegetables, fruits, and fruit juices were stated in grams per day. They were analysed as continuous variables (increments of 100 g/d for groups and 50 g/d or 10 g/d for subgroups), and as categorical variables using EPIC-wide quartiles (quartile 1 as reference) or EPIC-specific quartiles by sex, BMI categories, and physical activity status for subgroup analyses. Tests for linear trend were performed by attributing the median of each quartile as a score. Age was the primary time variable in all models. Entry time was age at recruitment and exit time was age at diagnosis of differentiated TC, death, or censoring date (loss of follow-up, end of follow-up), whichever occurred first. Two sets of models were used without (model A) and with (model B) adjustment for total energy intake. Model A1 was stratified by sex, age at recruitment (1-year interval) and centre. Model A2 was model A1 additionally adjusted for non-dietary variables: BMI, smoking status (never, former, current smoker, and unknown), education (primary, secondary, and unknown), physical activity (inactive, active, and unknown according to the Cambridge Physical Activity Index),21 type of menopause (pre-, peri-, post-, and surgical menopause), use of oral contraceptives (yes, no, and unknown), and fertility problems (yes, no, and unknown), since these reproductive factors were TC risk factors in our previous study.22 Model B1 was stratified by sex, age recruitment (1-year interval) and centre, and adjusted for total energy intake (kcal/day). Model B2 was model B1 additionally adjusted for non-dietary variables (as model A2) and dietary variables: total alcohol (g/day) intake. We also created an additional model (model B3) for the main exposure groups, which was model B2 mutually adjusted, when appropriate, for vegetables, fruits, and fruit juices, accordingly. The interpretation of models without total energy intake is focused on the impact of the effect of the absolute amount of compounds of F&V and fruit juices (e.g. vitamins, polyphenols, and contaminants). Whereas in the case of the models with total energy intake adjustment, the relevance is the relative amount compare to other compounds, like in a substitution model. Tests and graphs based on Schoenfeld residuals were used to assess proportional hazards assumptions, which were satisfied. Separate analyses were performed for TC subtypes: follicular and papillary tumours. Heterogeneity of risk between TC subtypes was assessed with the Wald test. Possible interactions with sex, smoking status, BMI (BMI<25 vs. BMI≥25), alcohol intake at recruitment (≤24 g/d vs. >24 g/d), and physical activity (inactive, active) were tested by including an interaction term in the multi-adjusted models. The Wald test was used to evaluate the heterogeneity of risk between BMI and physical activity categories. Sensitivity tests were performed i) excluding female participants from France, since they contributed to 37.2% of all differentiated TC cases among all female participants, and over-diagnosis in France could be relatively high;11 (ii) excluding participants who had diabetes or unknown diabetes status at baseline, because diabetes is a potential risk factor of TC and iii) excluding cases with a follow-up period below two years, since they could have changed their diets in the pre-diagnostic period. For all analyses, p-values <0.05 were considered as statistically significant and p-values >0.05 and <0.1 as borderline statistically significant. To account for multiple testing for the subgroups of F&V, Bonferroni correction was used and then results were considered statistically significant if P<0.05/23 (number of tests for the intakes of total F&V, vegetables, fruits, fruit juices and all subgroups)=0.002. All statistical analyses were performed with the R 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Calibration of dietary data

A second dietary measurement was taken from an 8% random sample of the cohort (36,994 participants) using a detailed computerized 24-h dietary recall (24-HDR) method23 to calibrate dietary measurements of vegetable, fruit, and fruit juice intake across countries and to correct for systematic overestimation or underestimation of dietary intakes.24 The 24-HDR values of these participants were regressed on the main dietary questionnaire values for vegetables, fruits, and fruit juices with adjustment for age at recruitment, centre, and total energy intake, and weighting by day of the week and season of the year during which the 24-HDR was collected. 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. The standard error of the calibrated coefficient was estimated with bootstrap sampling in the calibration and disease models and repeated 300 times.24

Results

The median (percentile 25th and 75th) intakes of total F&V, vegetables, fruits, and fruit juices were 391 g/d (250-576 g/d), 175 g/d (110-276 g/d), 194 g/d (106-314 g/d), and 20 g/d (1-94 g/d), respectively. A great heterogeneity of F&V consumption in both men and women among EPIC countries was observed with higher F&V intakes in Southern than in Northern EPIC countries(Table 1). Differentiated TC incidence was higher among women (89% of cases) and the most common subtype was papillary (80.3%), followed by follicular (14.6%), and NOS tumours (5.1%) (Table 1). The analysis of baseline characteristics according to quartiles of total intake of F&V showed that participants in the highest quartile were more likely to be older women, less educated, and less physically active, and to have higher total energy intake and lower tobacco and alcohol consumptions. Women in the highest quartile of F&V tended to be postmenopausal or to have undergone surgical menopause, to have more infertility problems, and to take less oral contraceptives at the baseline (Supplementary Table 1).

Four multivariable Cox models with different levels of adjustment (with and without total energy intake) were performed, showing similar results (difference below 10%) (Table 2 and

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Supplementary table 2). In the fully adjusted model (model B2), no association was observed between total intake of F&V and total differentiated TC risk for the highest vs. lowest quartile (HR: 0.89; 95% CI: 0.68-1.15; p-trend=0.44). No association was found with the intake of vegetables (HR: 0.89; 95% CI: 0.69-1.14; p-trend=0.56), or fruits (HR: 1.00; 95% CI: 0.79-1.26; p-trend=0.64). A borderline positive trend between fruit juice intake and total differentiated TC risk was detected (HR: 1.23; 95% CI: 0.98-1.53; p-trend=0.06). After calibration, results were unchanged. In separate analyses by TC type, null results were observed between all exposures and either papillary or follicular TC risk (Table 2). A further model (model B3) was also estimated mutually adjusting for the intake of fruits, vegetables or fruit juices when appropriate and results were practically identical to those in model B2 (Supplementary table 2). Sensitivity tests, excluding French participants, subject with diabetes at baseline, and cases with a follow-up below two years, showed results almost identical to those in the entire cohort (data not shown).

No association between any subgroups of F&V intake and total differentiated TC risk was found (Table 3). Associations with papillary and follicular TC risk were also evaluated. For every 10g/day of sprouts/stalk vegetables, the risk of follicular TC was significantly lowered for the observed data (HR: 0.72; 95% CI: 0.56-0.94; p-value=0.015) and for the calibrated data (HR: 0.56; 95% CI: 0.34-0.91%; p-value=0.020), but not for papillary TC risk. After applying the Bonferroni correction ($p<0.002$), the inverse association was no longer statistically significant. No associations were observed for any of the other subgroups of F&V with either papillary or follicular TC risk.

No interactions were observed between total intake of F&V and any of the tested potential confounding factors: sex (P for interaction=0.84), smoking status (P for interaction=0.58), BMI (P for interaction=0.37), alcohol (P for interaction=0.54), and physical activity (P for interaction=0.41). Although no heterogeneity was observed between sexes, separate analyses by sex were performed because of the large proportion of women with TC. The study of the association between total intake of F&V and TC risk showed similar results from the previous analyses for both women (HR: 0.88; 95% CI: 0.68-1.15; p-trend=0.34) and men (HR: 0.95; 95% CI: 0.42-2.12; p-trend=0.85) (data not tabulated). A statistically significant interaction between fruit juice intake and BMI (P for interaction=0.03) and borderline significant with physical activity (P for interaction=0.08) was detected. The highest quartile of fruit juice consumption was positively associated with TC risk among inactive participants (HR: 1.31; 95% CI: 0.99-1.72; p-trend=0.05) but not among active subjects (HR: 1.00; 95% CI: 0.70-1.42; p-trend=0.99); and in participants with BMI<25 (HR: 1.43; 95% CI: 1.08-1.89; p-trend=0.002), but not in those with BMI≥25 (HR: 1.06; 95% CI: 0.75-1.48; p-trend=0.99). Similar results were found for the analyses by TC subtypes, especially by BMI categories (Supplementary table 3).

Discussion

In the present study, we prospectively evaluated the association between total F&V and fruit juice intakes and differentiated TC risk. We did not observe any association between total F&V intake and either all differentiated, papillary, or follicular TC risk. Similar null results were also found in a Korean case-control study on mainly papillary TC cases (90%) among

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women.[25] Furthermore in our study, no associations with the consumption of either fruits or vegetables were observed; whereas a borderline statistical positive trend with fruit juice intake was detected.

A meta-analysis of 19 case-control studies[12] and a pooled-analysis of 11 case-control studies[26] summarized the associations between vegetable intake and TC risk, showing a weak inverse association with the intake of total vegetables and vegetables excluding cruciferous vegetables. An American cohort study of 300,000 participants (the NIH-AARP diet and health study) showed an impact of adolescent (12-13 years old) and midlife diet (10 years before recruitment when respondents were 41–62 years of age) on TC risk, with a significant inverse association of vegetable intake among women.[27] Although intakes of vegetables consumed by both Americans at midlife and our study population were comparable, we did not find any association between the intake of vegetables and the risk of differentiated TC either overall or by subtype.

In the present cohort study, we observed no association between differentiated TC risk and the consumption of cruciferous vegetables. Similar results were observed in two meta-analyses and one pooled-analysis.[12,26,28] However, in the most recent meta-analysis, a positive association was pointed out, after excluding studies evaluating only one type of cruciferous vegetables and hospital-based case-control studies.[16] The NIH-AARP diet and health study also showed a positive association with the intake of broccoli during midlife in men, however no other cruciferous vegetables were considered in the dietary questionnaire.[27] Overall, no association between the intake of vegetables and cruciferous vegetables and TC was observed in the last 5-10 years before diagnosis (i.e. middle and late adulthood), although potential relationships in earlier life stages, such as adolescence and young adulthood, could not be ruled out according to the results from the NHI-AARP study. Those results suggest that a diet rich in cruciferous vegetables during early adulthood could have an impact in the early development of TC, but not during the 5-10 years prior to TC diagnosis, which is the mean time of follow-up of TC cases in our study.

Overall, no associations were found with vegetable subclasses with overall, papillary or follicular TC risk. Some previous studies suggested inverse associations with raw vegetables,[25] green vegetables,[29] carrots,[29,30] green salad,[30] raw tomatoes,[31] turnips,[32] rutabagas,[32] and cassava.[33] However, these studies were relatively small (<400 TC cases) and had a retrospective design. Moreover these inverse associations have not been consistently observed in other similar studies and were not even suggested in our large cohort. In the analysis by TC type, there was an inverse association with sprouts/stalk vegetables but only for follicular TC risk (n=109 cases), although no longer after Bonferroni correction. In addition, sprouts/stalk vegetables (including asparagus, celery, fennel and leek) are a very heterogeneous group and are generally consumed in low amounts in Europe, and therefore the results could be due to chance.

In the current study, total fruit intake, as well as intake of fruit subtypes was not associated with TC risk. Although less information is available on this field, our findings are in concordance with the results of previous studies, including the meta-analysis of 19 case-control studies[12] and the American cohort study considering adolescent and midlife periods.

27 Some studies showed a special interest in citrus fruits because of their high content in antioxidants (such as vitamin C and flavonoids). A pooled-analysis of four Italian-based case-control studies showed an inverse association with TC risk.30 Both Greek and South Korean case-control studies reported inverse associations with the consumption of lemons31 and tangerines,25 respectively. However, in the present study, there was no association with citrus fruits intake, similarly to the NIH-AARP cohort where consumption of orange and tangelos was not associated with TC risk in any period.17

In the present study, a positive trend between the intake of fruit juices and TC risk was observed, especially in subjects with a BMI<25 or physically inactive. In the NIH-AARP cohort study, the consumption of orange and grapefruit juices was also associated with a higher risk of TC.17 In our study, fruit juices were mainly citrus juices (>61%), but most of them were commercial fruit juices and fruit nectars (62.3%) with a high sugar content. The contribution of fruit juices to total sugars varied from <2% in Mediterranean countries to 15% in Germany.34 In our study, we cannot differentiate between commercial fruit juice and fruit nectar (fruit juice with added sugars), and therefore we cannot evaluate the impact of the consumption of fruit juices with different amounts of sugar in the TC risk. Moreover, we cannot distinguish between fruit juices and vegetable juices in all participating countries, although vegetable juices are rarely consumed (only contributing to <2% of total juices in our study). Our results by BMI categories were in concordance with a recent study within EPIC, showing that the intake of sugar was positively associated with TC risk among people with a BMI <25.35 This finding could be partially due to a higher consumption of fruit juices in subjects with a BMI<25 (66.9 g/d) than with a BMI≥25 (60.4 g/d). However, the opposite results would be expected, since overweight is a major determinant of insulin resistance and hyperinsulinemia,36 which were associated with a higher prevalence of differentiated TC.37 Furthermore, after calibration, no differences in the association between fruit juice intake and TC by BMI were observed. This could be due to a higher under-reporting of fruit juice intake among overweight people. Therefore, we need to be cautious in the interpretation of these sub-analyses. In the analyses by physical activity status, the intake of fruit juices was positively associated with TC risk among inactive participants. It has been reported that physical activity significantly improves glycaemia and sensitivity to insulin, which have been associated with a higher risk of TC.37,38 Moreover, physical activity modifies female hormone levels,39 which may have a weak influence on TC risk. 22,40

On one hand, various components of F&V and fruit juices could exert a protective effect against TC. The intake of vitamins (in particular vitamin C and E, carotenoids), polyphenols and fibre has been related to a reduced risk of TC in some studies.41,42 Moreover, a deficiency in magnesium may be involved in the aetiology of some thyroid diseases.43 However the protective effects of F&V and fruit juices components are not consistent and several studies showed null results,17,35,44,45 or even positive associations [e.g., with beta-carotene,46 vitamin C47 and flavanones].17

On the other hand, F&V and fruit juices can also contain traces of chemical pesticides. A high exposure to organophosphate insecticides was associated with a higher TC incidence among spouses of pesticide applicators.48 Vegetables are also good sources of nitrates,

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accounting for 80% of their intake in Westernized diets.[49] They are involved in the formation of N-nitroso compounds, which are known carcinogens.[50] Indeed, nitrate intake has been positively associated with TC risk in two cohort studies.[51,52] Cruciferous vegetables contain large amounts of glucosinolates, which are a nutritional source of thiocyanates and isothiocyanates. Those molecules can block the action of carcinogenic substances and suppress the expression of neoplasia in initiated cancer cells,[53] but they also act as goitrogens,[13] promoting thyroid tumour growth in rats.[14,15]

Strengths of the EPIC study are its prospective design, its large number of cancer cases, and the wide range of F&V and fruit juice intake across participants from 10 European countries with standardized information on diet and lifestyle exposures. Several limitations have to be taken into account. Although EPIC is a large study, participants are not representative of the whole population in most of the countries because of the criteria of recruitment, and therefore the results are not totally generalizable to general population. The measurement error in the estimation of F&V and fruit juice intake by dietary questionnaires may have attenuated our findings, although the use of the calibrated F&V and fruit juice data, obtained from the standardized 24-HDR, did not alter the results. As discussed above, we do not have data on fruit juices and fruit nectars separately. Dietary and lifestyle habits during the follow-up period are not available in EPIC, although diet is relatively stable in adult populations through the years.

To conclude, in the present study, no association with differentiated TC risk was observed for the consumption of total F&V, vegetables, fruits, and their subgroups. This result might be explained by a counterbalance between pro- and anti-carcinogenic effects of their components. However, fruit juice intake was associated with an increased risk of differentiated TC, possibly due to the high sugar content. Our study supports having a diverse intake of F&V, but not consuming too much fruit juice, especially those rich in sugars. Further prospective studies are warranted to confirm these relationships between fruit juice intake and TC risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

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

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Novelty and Impact of the Work

This large prospective cohort does not support any association between the consumption of vegetable, fruit and any individual type of vegetable or fruit and differentiated thyroid carcinoma risk, overall and by histologic type (papillary and follicular tumours). However, a positive trend with fruit juice intake was observed, possibly related to its high sugar content

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Table 1

Distribution of participants, thyroid cancer cases according to cancer type and intakes of vegetables, fruits and fruit juices by sex across the EPIC countries

Country	All	Person-years	Differentiated thyroid carcinoma cases				Total vegetables and fruits (g/d)	Vegetables (g/d)	fruits (g/d)	Fruit juices (g/d)
			Overall	Papillary	Follicular	NOS	Median (25th-75th)	Median (25th-75th)	Median (25th-75th)	Median (25th-75th)
WOMEN										
France	67,391	869,292	248	227	19	2	510 (379-669)	264 (189-356)	234 (145-332)	18 (0-83)
Italy	30,511	434,977	106	81	16	9	483 (353-638)	162 (109-232)	306 (210-426)	8 (0-38)
Spain	24,846	398,818	74	62	11	1	523 (363-714)	216 (138-315)	279 (169-429)	1 (0-6)
United Kingdom	52,565	793,526	39	24	10	5	496 (359-671)	256 (186-347)	223 (138-338)	51 (9-120)
The Netherlands	26,910	384,225	13	10	3	0	325 (232-432)	126 (98-162)	187 (119-278)	56 (13-137)
Greece	15,229	168,454	28	22	1	5	753 (586-945)	412 (317-527)	332 (233-443)	24 (6-47)
Germany	27,373	284,894	67	47	18	2	254 (189-344)	117 (89-156)	118 (88-198)	114 (38-248)
Sweden	26,365	442,218	29	20	4	5	310 (206-434)	119 (70-184)	175 (109-265)	16 (0-89)
Denmark	28,714	432,361	26	18	8	0	358 (244-504)	172 (112-244)	170 (98-274)	9 (2-43)
Norway	33,972	452,152	36	31	4	1	268 (185-378)	126 (87-179)	130 (72-212)	43 (0-107)
TOTAL	333,876	4,660,917	666	542	94	30	415 (274-594)	186 (118-286)	210 (120-324)	21 (1-95)
MEN										
Italy	14,032	195,955	21	16	3	2	460 (332-620)	147 (99-211)	296 (195-423)	13 (0-38)
Spain	15,138	239,107	6	4	2	0	540 (361-751)	240 (150-353)	272 (145-435)	1 (0-5)
United Kingdom	22,850	329,232	5	5	0	0	411 (291-564)	223 (159-306)	172 (100-270)	17 (8-120)
The Netherlands	9,627	140,422	4	2	1	1	247 (176-348)	115 (88-148)	125 (66-224)	40 (7-108)
Greece	10,815	112,787	8	6	0	2	798 (631-992)	451 (356-565)	334 (233-450)	26 (7-61)
Germany	21,178	219,542	15	11	3	1	216 (160-293)	108 (81-142)	98 (65-160)	101 (32-224)
Sweden	22,301	358,848	10	5	3	2	214 (128-332)	82 (40-142)	119 (60,6-198)	13 (0-71)
Denmark	26,291	382,654	13	10	3	1	281 (185-402)	151 (97-216)	115 (54-192)	8 (2-43)
TOTAL	228,875	1,978,547	82	59	15	8	328 (203-523)	151 (94-248)	156 (82-280)	17 (1-77)
ALL	476,108	6,639,464	748	601	109	38	391 (250-576)	175 (110-276)	194 (106-314)	20 (1-94)

Abbreviations: NOS not otherwise specified

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Table 1

Hazard ratios and 95% confidence intervals for overall, papillary and follicular thyroid cancer according to quartile of intake of vegetables, fruits and fruit juices in the EPIC study

	Intake (g/d)	Overall differentiated TC			Papillary TC			Follicular TC			P-value[c]
		No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	
Total vegetables and fruits											
Quartile 1	<250	137	1 (ref)	1 (ref)	100	1 (ref)	1 (ref)	29	1 (ref)	1 (ref)	
Quartile 2	250-391	163	0.93 (0.73-1.17)	0.91 (0.72-1.16)	131	1.00 (0.76-1.31)	0.98 (0.74-1.28)	22	0.66 (0.37-1.17)	0.67 (0.38-1.20)	
Quartile 3	392-576	226	1.03 (0.81-1.30)	1.00 (0.78-1.27)	190	1.11 (0.85-1.45)	1.06 (0.81-1.40)	31	0.92 (0.52-1.62)	0.96 (0.54-1.71)	
Quartile 4	>576	222	0.93 (0.73-1.20)	0.89 (0.68-1.15)	180	0.98 (0.85-1.45)	0.91 (0.68-1.22)	27	0.83 (0.45-1.56)	0.84 (0.43-1.62)	
P-trend			0.69	0.44		0.77	0.43		0.87	0.90	
Observed continuous (per 100g/d)			1.01 (0.97-1.04)	0.99 (0.97-1.03)		1.00 (0.97-1.04)	1.00 (0.96-1.03)		1.05 (0.96-1.13)	1.05 (0.97-1.15)	0.86
Calibrated continuous (per 100g/d)			1.03 (0.96-1.11)	1.01 (0.94-1.09)		1.02 (0.94-1.11)	1.00 (0.91-1.09)		1.15 (0.96-1.37)	1.15 (0.95-1.39)	0.20
Vegetables											
Quartile 1	<110	160	1 (ref)	1 (ref)	122	1 (ref)	1 (ref)	26	1 (ref)	1 (ref)	
Quartile 2	110-175	164	0.87 (0.69-1.09)	0.87 (0.69-1.08)	124	0.84 (0.65-1.09)	0.83 (0.64-1.08)	28	1.01 (0.58-1.75)	1.05 (0.60-1.83)	
Quartile 3	176-276	204	0.93 (0.74-1.17)	0.93 (0.74-1.17)	169	0.94 (0.73-1.22)	0.92 (0.71-1.20)	32	1.24 (0.71-2.19)	1.34 (0.75-2.39)	
Quartile 4	>276	220	0.91 (0.71-1.16)	0.89 (0.69-1.14)	186	0.92 (0.70-1.21)	0.88 (0.66-1.17)	23	1.04 (0.54-2.00)	1.12 (0.57-2.22)	
P-trend			0.69	0.56		0.89	0.66		0.87	0.71	
Observed continuous (per 100g/d)			0.99 (0.99-1.00)	0.98 (0.92-1.04)		0.99 (0.92-1.05)	0.97 (0.91-1.04)		1.07 (0.91-1.26)	1.09 (0.92-1.29)	0.83
Calibrated continuous (per 100g/d)			1.02 (0.84-1.24)	0.99 (0.81-1.21)		1.00 (0.80-1.25)	0.96 (0.77-1.20)		1.31 (0.81-2.10)	1.34 (0.94-2.16)	0.13
Fruits											
Quartile 1	<106	149	1 (ref)	1 (ref)	114	1 (ref)	1 (ref)	28	1 (ref)	1 (ref)	
Quartile 2	106-194	162	0.91 (0.73-1.15)	0.90 (0.71-1.13)	133	0.97 (0.75-1.25)	0.95 (0.73-1.22)	23	0.74 (0.42-1.31)	0.74 (0.42-1.30)	
Quartile 3	195-314	194	0.90 (0.72-1.13)	0.88 (0.70-1.10)	157	0.94 (0.73-1.22)	0.91 (0.70-1.17)	24	0.69 (0.39-1.23)	0.70 (0.39-1.25)	
Quartile 4	>314	243	1.04 (0.83-1.31)	1.00 (0.79-1.26)	197	1.08 (0.84-1.39)	1.02 (0.79-1.33)	34	1.01 (0.58-1.78)	0.99 (0.55-1.78)	
P-trend			0.43	0.64		0.41	0.68		0.70	0.73	
Observed continuous (per 100g/d)			1.02 (0.97-1.06)	1.00 (0.97-1.05)		1.02 (0.97-1.06)	1.01 (0.96-1.05)		1.05 (0.94-1.17)	1.05 (0.94-1.18)	0.88
Calibrated continuous (per 100g/d)			1.04 (0.95-1.13)	1.02 (0.93-1.12)		1.03 (0.93-1.13)	1.00 (0.91-1.11)		1.15 (0.92-1.42)	1.15 (0.91-1.43)	0.28

	Intake (g/d)	Overall differentiated TC			Papillary TC			Follicular TC			P-value[c]
		No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	No of cases	Model A1[a] HR (95% CI)	Model B2[b] HR (95% CI)	
Fruit juices											
Quartile 1	<1	205	1(Ref)	1(Ref)	172	1 (Ref)	1 (Ref)	24	1 (Ref)	1 (Ref)	
Quartile 2	1-20	151	1.03 (0.82-1.29)	1.03 (0.82-1.29)	121	1.38 (0.75-2.54)	1.40 (0.76-2.57)	25	1.01 (0.78-1.30)	1.00 (0.78-1.30)	
Quartile 3	21-94	207	1.14 (0.93-1.41)	1.16 (0.94-1.43)	168	1.53 (0.85-2.74)	1.59 (0.88-2.86)	29	1.10 (0.88-1.39)	1.11 (0.88-1.40)	
Quartile 4	>94	185	1.19 (0.96-1.48)	1.23 (0.98-1.53)	140	1.57 (0.87-2.85)	1.69 (0.92-3.08)	31	1.10 (0.87-1.41)	1.12 (0.88-1.43)	
P-trend			0.10	0.06		0.28	0.19		0.41	0.35	
Observed continuous (per 50g/d)			1.02 (0.99-1.05)	1.02 (0.99-1.06)		1.02 (0.94-1.10)	1.02 (0.94-1.11)		1.02 (0.98-1.06)	1.02 (0.98-1.06)	0.37
Calibrated continuous (per 50g/d)			1.04 (0.95-1.14)	0.99 (0.92-1.08)		1.01 (0.92-1.10)	1.01 (0.92-1.10)		0.98 (0.82-1.16)	0.98 (0.82-1.16)	0.65

Abbreviations: HR Hazard Ratio; CI confidence interval; TC thyroid carcinoma

[a] Model A1: Cox model stratified by centre, age at baseline and sex,

[b] Model B2: Model A1 additionally adjusted for body mass index, smoking status, education level, physical activity, total energy and alcohol intake. In women, also adjusted for menopausal status and type, oral contraceptive use, and infertility problems.

[c] P for heterogeneity using the Wald test.

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Table 1

Hazard ratios and 95% confidence intervals for overall, papillary and follicular thyroid cancer according to continuous variable of intake of subgroups of vegetables and fruits in the EPIC study

	Overall differentiated TC (748 cases)		Papillary TC (601 cases)		Follicular TC (109 cases)		P-heterogeneity[d]	
	Observed[b] HR (95% CI)	Calibrated[c] HR (95% CI)	Observed[b] HR (95% CI)	Calibrated[c] HR (95% CI)	Observed[b] HR (95% CI)	Calibrated[c] HR (95% CI)	Observed	Calibrated
Vegetables								
Leafy vegetables (per 50g/d)[a]	0.98 (0.88-1.09)	1.01 (0.69-1.47)	0.96 (0.85-1.08)	0.94 (0.62-1.43)	1.15 (0.86-1.53)	1.56 (0.56-4.34)	0.25	0.34
Fruiting vegetables (per 50g/d)	1.02 (0.96-1.09)	1.00 (0.84-1.20)	1.03 (0.96-1.10)	1.01 (0.83-1.24)	1.06 (0.89-1.27)	1.13 (0.72-1.79)	0.27	0.55
Root vegetables (per 50g/d)	1.04 (0.90-1.18)	1.16 (0.84-1.58)	1.06 (0.91-1.23)	1.24 (0.88-1.74)	1.04 (0.73-1.47)	1.11 (0.52-2.37)	0.62	0.7
Cabbages (per 50g/d)	1.02 (0.88-1.19)	1.17 (0.70-1.96)	1.09 (0.92-1.28)	1.34 (0.75-2.40)	0.81 (0.51-1.28)	0.99 (0.28-3.57)	0.64	0.52
Mushrooms (per 10g/d)	1.03 (0.93-1.14)	1.02 (0.67-1.56)	1.06 (0.95-1.17)	1.03 (0.63-1.68)	0.78 (0.53-1.14)	0.82 (0.25-2.67)	0.24	0.45
Grain and pod vegetables (per 10g/d)	1.02 (0.95-1.09)	1.04 (0.80-1.36)	1.04 (0.97-1.12)	1.15 (0.86-1.53)	1.04 (0.86-1.24)	0.83 (0.40-1.74)	0.3	0.22
Onion/garlic (per 10g/d)	1.00 (0.93-1.09)	0.97 (0.78-1.21)	1.01 (0.92-1.11)	0.97 (0.76-1.25)	1.02 (0.84-1.23)	0.97 (0.55-1.72)	0.49	1.00
Sprouts/stalk vegetables (per 10g/d)	0.96 (0.90-1.03)	0.91 (0.75-1.09)	1.00 (0.93-1.07)	1.01 (0.82-1.24)	0.72 (0.56-0.94)[e]	0.56 (0.34-0.91)[e]	0.03	<0.001
Fruits								
Citrus fruits (per 50g/d)	0.98 (0.92-1.05)	1.02 (0.89-1.15)	0.97 (0.91-1.05)	1.00 (0.87-1.15)	1.11 (0.96-1.29)	1.26 (0.95-1.68)	0.54	0.17
Apples and pears (per 50g/d)	0.98 (0.93-1.03)	0.96 (0.89-1.04)	0.98 (0.92-1.04)	0.96 (0.88-1.05)	0.97 (0.85-1.11)	0.92 (0.76-1.12)	0.51	0.6
Berries (per 50g/d)	1.03 (0.87-1.21)	1.07 (0.81-1.41)	1.08 (0.91-1.29)	1.17 (0.87-1.58)	0.86 (0.52-1.42)	0.72 (0.30-1.74)	0.15	0.05
Stone fruits (per 50g/d)	1.04 (0.96-1.12)	1.10 (0.90-1.33)	1.01 (0.93-1.11)	1.05 (0.85-1.30)	1.25 (0.80-1.04)	1.40 (0.84-2.33)	0.81	0.34
Banana (per 50g/d)	0.94 (0.81-1.09)	0.82 (0.59-1.13)	0.97 (0.82-1.14)	0.91 (0.63-1.31)	0.90 (0.61-1.30)	0.64 (0.29-1.40)	0.73	0.12
Other fruits (per 50g/d)	1.06 (0.96-1.17)	1.05 (0.80-1.36)	1.07 (0.96-1.19)	1.11 (0.83-1.47)	0.98 (0.69-1.40)	0.74 (0.31-1.75)	0.18	0.10

Abbreviations: HR Hazard Ratio; CI confidence interval; TC thyroid carcinoma

[a] excluding Norway (n=33 972 participants)

[b] Model B2: Cox model stratified by centre, age at baseline and sex, and adjusted for body mass index, smoking status, education level, physical activity, total energy and alcohol intake. In women, also adjusted for menopausal status and type, oral contraceptive use, and infertility problems.

[c] Model B2 applied to calibrated variables

[d] P for heterogeneity using the Wald test.

[e] After applying the Bonferroni correction, the inverse association was no longer statistically significant.