

# 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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**Abbreviations:** 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.

1 **ABSTRACT**

2 Fruit and vegetable (F&V) intake is considered as probably protective against overall cancer  
3 risk, but results in previous studies are not consistent for thyroid cancer (TC). The purpose of  
4 this study is to examine the association between the consumption of fruits, vegetables, fruit  
5 juices and differentiated thyroid cancer risk within the European Prospective Investigation  
6 into Cancer and Nutrition (EPIC) study. The EPIC study is a cohort including over half a  
7 million participants, recruited between 1991 and 2000. During a mean follow-up of 14 years,  
8 748 incident first primary differentiated TC cases were identified. F&V and fruit juice intakes  
9 were assessed through validated country-specific dietary questionnaires. Hazard ratios (HRs)  
10 and 95% confidence intervals (CIs) were estimated using Cox regression models adjusted for  
11 potential confounding factors. Comparing the highest vs. lowest quartile of intake,  
12 differentiated TC risk was not associated with intakes of total F&V (HR: 0.89; 95% CI: 0.68-  
13 1.15; p-trend=0.44), vegetables (HR: 0.89; 95% CI: 0.69-1.14; p-trend=0.56), or fruit (HR:  
14 1.00; 95% CI: 0.79-1.26; p-trend=0.64). No significant association was observed with any  
15 individual type of vegetable or fruit. However, there was a positive borderline trend with fruit  
16 juice intake (HR: 1.23; 95% CI: 0.98-1.53; p-trend=0.06). This study did not find any  
17 significant association between F&V intakes and differentiated TC risk; however a positive  
18 trend with fruit juice intake was observed, possibly related to its high sugar content.

19

## 20 INTRODUCTION

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

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

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

45

## 46 **MATERIAL AND METHODS**

### 47 *Study population*

48 EPIC is a multicentre prospective cohort study principally designed to investigate the  
49 relationships between diet and other environmental factors and cancer risk. The study design  
50 has been explained in detail previously.<sup>19,20</sup> In brief, EPIC enrolled more than half a million  
51 participants, 70% women, mostly aged between 35 and 70 years old from 23 centres in 10  
52 western European countries (Denmark, France, Germany, Greece, Italy, Norway, Sweden,  
53 Spain, the Netherlands, and the United Kingdom) during the period 1991-2000. All  
54 participants gave their written informed consent, and the Internal Review Boards of the IARC  
55 and all ethical committees from participating centres approved the project.

### 56 *Dietary assessment*

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

67 The analysed food groups were vegetables (potatoes and legumes were not included), fresh  
68 fruits (excluding nuts, olives, and seeds), and total juices or fruit juices (including citrus fruit

69 juices, non-citrus fruit juices, vegetable juices and fruit nectars). Vegetable juices were rarely  
70 consumed (<2% of total juices) and this item was only recorded in the dietary questionnaires  
71 of 3 countries; for this reason we have simplified and used the term fruit juices instead of total  
72 juices. Total intake of F&V was calculated as the sum of fruits and vegetables, excluding fruit  
73 juices because of their large differences in nutritional composition compared to F&V.<sup>18</sup>  
74 Subgroups of vegetables and fruits were also considered: leafy vegetables, fruiting vegetables,  
75 root vegetables, cabbages, mushrooms, grain and pod vegetables, onion/garlic, sprouts/stalk  
76 vegetables, citrus fruits, hard fruits (apples and pears), berries (strawberries, grapes,  
77 blueberries), stone fruits (peach, nectarine, apricot, plum, cherry), banana, and other fruits  
78 (fig, kiwi, melon, watermelon, pineapple). Details about the composition of the subgroups are  
79 given elsewhere.<sup>18</sup>

#### 80 *Follow-up and case ascertainment*

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

91 Of the 857 TC cases, anaplastic (n=9), medullary (n=37), lymphoma (n=1) forms and “other  
92 morphologies” (n=5) were excluded. Moreover, 29,332 participants (including 45  
93 differentiated TC cases) were excluded from the initial database because of missing or null

94 follow-time or having a prevalent cancer other than non-melanoma skin cancer. Further 1,277  
95 and 14,555 participants (including 12 differentiated TC cases) were also excluded because  
96 their lifestyle and dietary data were not complete or coherent (they were in the top or the  
97 bottom 1% of the distribution of the total energy intake to energy requirement ratio),  
98 respectively. Finally, 748 first primary incident differentiated TC cases were considered: 601  
99 papillary TCs, 109 follicular TCs, and 38 not otherwise specified (NOS) TCs, most likely  
100 papillary TCs. A total of 142,232 men and 333,876 women were included in the present  
101 study.

## 102 *Statistical analysis*

103 Cox proportional hazard models were used to estimate hazard ratios (HR) and 95%  
104 confidence intervals (CI). Intakes of vegetables, fruits, and fruit juices were stated in grams  
105 per day. They were analysed as continuous variables (increments of 100 g/d for groups and 50  
106 g/d or 10 g/d for subgroups), and as categorical variables using EPIC-wide quartiles (quartile  
107 1 as reference) or EPIC-specific quartiles by sex, BMI categories, and physical activity status  
108 for subgroup analyses. Tests for linear trend were performed by attributing the median of each  
109 quartile as a score. Age was the primary time variable in all models. Entry time was age at  
110 recruitment and exit time was age at diagnosis of differentiated TC, death, or censoring date  
111 (loss of follow-up, end of follow-up), whichever occurred first. Two sets of models were used  
112 without (model A) and with (model B) adjustment for total energy intake. Model A1 was  
113 stratified by sex, age at recruitment (1-year interval) and centre. Model A2 was model A1  
114 additionally adjusted for non-dietary variables: BMI, smoking status (never, former, current  
115 smoker, and unknown), education (primary, secondary, and unknown), physical activity  
116 (inactive, active, and unknown according to the Cambridge Physical Activity Index),<sup>21</sup> type of  
117 menopause (pre-, peri-, post-, and surgical menopause), use of oral contraceptives (yes, no,  
118 and unknown), and fertility problems (yes, no, and unknown), since these reproductive factors

119 were TC risk factors in our previous study.<sup>22</sup> Model B1 was stratified by sex, age recruitment  
120 (1-year interval) and centre, and adjusted for total energy intake (kcal/day). Model B2 was  
121 model B1 additionally adjusted for non-dietary variables (as model A2) and dietary variables:  
122 total alcohol (g/day) intake. We also created an additional model (model B3) for the main  
123 exposure groups, which was model B2 mutually adjusted, when appropriate, for vegetables,  
124 fruits, and fruit juices, accordingly. The interpretation of models without total energy intake is  
125 focused on the impact of the effect of the absolute amount of compounds of F&V and fruit  
126 juices (e.g. vitamins, polyphenols, and contaminants). Whereas in the case of the models with  
127 total energy intake adjustment, the relevance is the relative amount compare to other  
128 compounds, like in a substitution model. Tests and graphs based on Schoenfeld residuals were  
129 used to assess proportional hazards assumptions, which were satisfied. Separate analyses were  
130 performed for TC subtypes: follicular and papillary tumours. Heterogeneity of risk between  
131 TC subtypes was assessed with the Wald test. Possible interactions with sex, smoking status,  
132 BMI (BMI<25 vs. BMI≥25), alcohol intake at recruitment ( $\leq 24$  g/d vs.  $>24$  g/d), and physical  
133 activity (inactive, active) were tested by including an interaction term in the multi-adjusted  
134 models. The Wald test was used to evaluate the heterogeneity of risk between BMI and  
135 physical activity categories. Sensitivity tests were performed i) excluding female participants  
136 from France, since they contributed to 37.2% of all differentiated TC cases among all female  
137 participants, and over-diagnosis in France could be relatively high;<sup>11</sup> (ii) excluding  
138 participants who had diabetes or unknown diabetes status at baseline, because diabetes is a  
139 potential risk factor of TC and iii) excluding cases with a follow-up period below two years,  
140 since they could have changed their diets in the pre-diagnostic period. For all analyses, p-  
141 values  $<0.05$  were considered as statistically significant and p-values  $>0.05$  and  $<0.1$  as  
142 borderline statistically significant. To account for multiple testing for the subgroups of F&V,  
143 Bonferroni correction was used and then results were considered statistically significant if

144 P<0.05/23 (number of tests for the intakes of total F&V, vegetables, fruits, fruit juices and all  
145 subgroups)=0.002. All statistical analyses were performed with the R 3.3.1 software (R  
146 Foundation for Statistical Computing, Vienna, Austria).

### 147 *Calibration of dietary data*

148 A second dietary measurement was taken from an 8% random sample of the cohort (36,994  
149 participants) using a detailed computerized 24-h dietary recall (24-HDR) method<sup>23</sup> to  
150 calibrate dietary measurements of vegetable, fruit, and fruit juice intake across countries and  
151 to correct for systematic overestimation or underestimation of dietary intakes.<sup>24</sup> The 24-HDR  
152 values of these participants were regressed on the main dietary questionnaire values for  
153 vegetables, fruits, and fruit juices with adjustment for age at recruitment, centre, and total  
154 energy intake, and weighting by day of the week and season of the year during which the 24-  
155 HDR was collected. Zero consumption values in the main dietary questionnaires were  
156 excluded in the regression calibration models, and a zero was directly imputed as a corrected  
157 value. Country and sex-specific calibration models were used to obtain individual predicted  
158 values of dietary exposure for all participants. Cox regression models were then run using the  
159 predicted (calibrated) values for each individual on a continuous scale. The standard error of  
160 the calibrated coefficient was estimated with bootstrap sampling in the calibration and disease  
161 models and repeated 300 times.<sup>24</sup>

## 162 **RESULTS**

163 The median (percentile 25<sup>th</sup> and 75<sup>th</sup>) intakes of total F&V, vegetables, fruits, and fruit juices  
164 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  
165 g/d), respectively. A great heterogeneity of F&V consumption in both men and women  
166 among EPIC countries was observed with higher F&V intakes in Southern than in Northern  
167 EPIC countries(**Table 1**). Differentiated TC incidence was higher among women (89% of  
168 cases) and the most common subtype was papillary (80.3%), followed by follicular (14.6%),

169 and NOS tumours (5.1%) (Table 1). The analysis of baseline characteristics according to  
170 quartiles of total intake of F&V showed that participants in the highest quartile were more  
171 likely to be older women, less educated, and less physically active, and to have higher total  
172 energy intake and lower tobacco and alcohol consumptions. Women in the highest quartile of  
173 F&V tended to be postmenopausal or to have undergone surgical menopause, to have more  
174 infertility problems, and to take less oral contraceptives at the baseline (**Supplementary**  
175 **Table 1**).

176 Four multivariable Cox models with different levels of adjustment (with and without total  
177 energy intake) were performed, showing similar results (difference below 10%) (**Table 2 and**  
178 **Supplementary table 2**). In the fully adjusted model (model B2), no association was  
179 observed between total intake of F&V and total differentiated TC risk for the highest vs.  
180 lowest quartile (HR: 0.89; 95% CI: 0.68-1.15; p-trend=0.44). No association was found with  
181 the intake of vegetables (HR: 0.89; 95% CI: 0.69-1.14; p-trend=0.56), or fruits (HR: 1.00;  
182 95% CI: 0.79-1.26; p-trend=0.64). A borderline positive trend between fruit juice intake and  
183 total differentiated TC risk was detected (HR: 1.23; 95% CI: 0.98-1.53; p-trend=0.06). After  
184 calibration, results were unchanged. In separate analyses by TC type, null results were  
185 observed between all exposures and either papillary or follicular TC risk (Table 2). A further  
186 model (model B3) was also estimated mutually adjusting for the intake of fruits, vegetables or  
187 fruit juices when appropriate and results were practically identical to those in model B2  
188 (Supplementary table 2). Sensitivity tests, excluding French participants, subject with diabetes  
189 at baseline, and cases with a follow-up below two years, showed results almost identical to  
190 those in the entire cohort (data not shown).

191 No association between any subgroups of F&V intake and total differentiated TC risk was  
192 found (**Table 3**). Associations with papillary and follicular TC risk were also evaluated. For  
193 every 10g/day of sprouts/stalk vegetables, the risk of follicular TC was significantly lowered

194 for the observed data (HR: 0.72; 95% CI: 0.56-0.94; p-value=0.015) and for the calibrated  
195 data (HR: 0.56; 95% CI: 0.34-0.91%; p-value=0.020), but not for papillary TC risk. After  
196 applying the Bonferroni correction (p<0.002), the inverse association was no longer  
197 statistically significant. No associations were observed for any of the other subgroups of F&V  
198 with either papillary or follicular TC risk.

199 No interactions were observed between total intake of F&V and any of the tested potential  
200 confounding factors: sex (P for interaction=0.84), smoking status (P for interaction=0.58),  
201 BMI (P for interaction=0.37), alcohol (P for interaction=0.54), and physical activity (P for  
202 interaction=0.41). Although no heterogeneity was observed between sexes, separate analyses  
203 by sex were performed because of the large proportion of women with TC. The study of the  
204 association between total intake of F&V and TC risk showed similar results from the previous  
205 analyses for both women (HR: 0.88; 95% CI: 0.68-1.15; p-trend=0.34) and men (HR: 0.95;  
206 95% CI: 0.42-2.12; p-trend=0.85) (data not tabulated). A statistically significant interaction  
207 between fruit juice intake and BMI (P for interaction=0.03) and borderline significant with  
208 physical activity (P for interaction=0.08) was detected. The highest quartile of fruit juice  
209 consumption was positively associated with TC risk among inactive participants (HR: 1.31;  
210 95% CI: 0.99-1.72; p-trend=0.05) but not among active subjects (HR: 1.00; 95% CI: 0.70-  
211 1.42; p-trend=0.99); and in participants with BMI<25 (HR: 1.43; 95% CI: 1.08-1.89; p-  
212 trend=0.002), but not in those with BMI≥25 (HR: 1.06; 95% CI: 0.75-1.48; p-trend=0.99).  
213 Similar results were found for the analyses by TC subtypes, especially by BMI categories  
214 (**Supplementary table 3**).

## 215 **DISCUSSION**

216 In the present study, we prospectively evaluated the association between total F&V and fruit  
217 juice intakes and differentiated TC risk. We did not observe any association between total  
218 F&V intake and either all differentiated, papillary, or follicular TC risk. Similar null results

219 were also found in a Korean case-control study on mainly papillary TC cases (90%) among  
220 women.<sup>25</sup> Furthermore in our study, no associations with the consumption of either fruits or  
221 vegetables were observed; whereas a borderline statistical positive trend with fruit juice intake  
222 was detected.

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

233 In the present cohort study, we observed no association between differentiated TC risk and  
234 the consumption of cruciferous vegetables. Similar results were observed in two meta-  
235 analyses and one pooled-analysis.<sup>12,26,28</sup> However, in the most recent meta-analysis, a positive  
236 association was pointed out, after excluding studies evaluating only one type of cruciferous  
237 vegetables and hospital-based case-control studies.<sup>16</sup> The NIH-AARP diet and health study  
238 also showed a positive association with the intake of broccoli during midlife in men, however  
239 no other cruciferous vegetables were considered in the dietary questionnaire.<sup>27</sup> Overall, no  
240 association between the intake of vegetables and cruciferous vegetables and TC was observed  
241 in the last 5-10 years before diagnosis (i.e. middle and late adulthood), although potential  
242 relationships in earlier life stages, such as adolescence and young adulthood, could not be  
243 ruled out according to the results from the NHI-AARP study. Those results suggest that a diet

244 rich in cruciferous vegetables during early adulthood could have an impact in the early  
245 development of TC, but not during the 5-10 years prior to TC diagnosis, which is the mean  
246 time of follow-up of TC cases in our study.

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

258 In the current study, total fruit intake, as well as intake of fruit subtypes was not associated  
259 with TC risk. Although less information is available on this field, our findings are in  
260 concordance with the results of previous studies, including the meta-analysis of 19 case-  
261 control studies<sup>12</sup> and the American cohort study considering adolescent and midlife periods.<sup>27</sup>  
262 Some studies showed a special interest in citrus fruits because of their high content in  
263 antioxidants (such as vitamin C and flavonoids). A pooled-analysis of four Italian-based case-  
264 control studies showed an inverse association with TC risk.<sup>30</sup> Both Greek and South Korean  
265 case-control studies reported inverse associations with the consumption of lemons<sup>31</sup> and  
266 tangerines,<sup>25</sup> respectively. However, in the present study, there was no association with citrus  
267 fruits intake, similarly to the NIH-AARP cohort where consumption of orange and tangelos  
268 was not associated with TC risk in any period.<sup>17</sup>

269 In the present study, a positive trend between the intake of fruit juices and TC risk was  
270 observed, especially in subjects with a BMI<25 or physically inactive. In the NIH-AARP  
271 cohort study, the consumption of orange and grapefruit juices was also associated with a  
272 higher risk of TC.<sup>17</sup> In our study, fruit juices were mainly citrus juices (>61%), but most of  
273 them were commercial fruit juices and fruit nectars (62.3%) with a high sugar content. The  
274 contribution of fruit juices to total sugars varied from <2% in Mediterranean countries to 15%  
275 in Germany.<sup>34</sup> In our study, we cannot differentiate between commercial fruit juice and fruit  
276 nectar (fruit juice with added sugars), and therefore we cannot evaluate the impact of the  
277 consumption of fruit juices with different amounts of sugar in the TC risk. Moreover, we  
278 cannot distinguish between fruit juices and vegetable juices in all participating countries,  
279 although vegetable juices are rarely consumed (only contributing to <2% of total juices in our  
280 study). Our results by BMI categories were in concordance with a recent study within EPIC,  
281 showing that the intake of sugar was positively associated with TC risk among people with a  
282 BMI <25.<sup>35</sup> This finding could be partially due to a higher consumption of fruit juices in  
283 subjects with a BMI<25 (66.9 g/d) than with a BMI≥25 (60.4 g/d). However, the opposite  
284 results would be expected, since overweight is a major determinant of insulin resistance and  
285 hyperinsulinemia,<sup>36</sup> which were associated with a higher prevalence of differentiated TC.<sup>37</sup>  
286 Furthermore, after calibration, no differences in the association between fruit juice intake and  
287 TC by BMI were observed. This could be due to a higher under-reporting of fruit juice intake  
288 among overweight people. Therefore, we need to be cautious in the interpretation of these  
289 sub-analyses. In the analyses by physical activity status, the intake of fruit juices was  
290 positively associated with TC risk among inactive participants. It has been reported that  
291 physical activity significantly improves glycaemia and sensitivity to insulin, which have been  
292 associated with a higher risk of TC.<sup>37,38</sup> Moreover, physical activity modifies female hormone  
293 levels,<sup>39</sup> which may have a weak influence on TC risk.<sup>22,40</sup>

294 On one hand, various components of F&V and fruit juices could exert a protective effect  
295 against TC. The intake of vitamins (in particular vitamin C and E, carotenoids), polyphenols  
296 and fibre has been related to a reduced risk of TC in some studies.<sup>41,42</sup> Moreover, a deficiency  
297 in magnesium may be involved in the aetiology of some thyroid diseases.<sup>43</sup> However the  
298 protective effects of F&V and fruit juices components are not consistent and several studies  
299 showed null results,<sup>17,35,44,45</sup> or even positive associations [e.g., with beta-carotene,<sup>46</sup> vitamin  
300 C<sup>47</sup> and flavanones].<sup>17</sup>

301 On the other hand, F&V and fruit juices can also contain traces of chemical pesticides. A high  
302 exposure to organophosphate insecticides was associated with a higher TC incidence among  
303 spouses of pesticide applicators.<sup>48</sup> Vegetables are also good sources of nitrates, accounting for  
304 80% of their intake in Westernized diets.<sup>49</sup> They are involved in the formation of N-nitroso  
305 compounds, which are known carcinogens.<sup>50</sup> Indeed, nitrate intake has been positively  
306 associated with TC risk in two cohort studies.<sup>51,52</sup> Cruciferous vegetables contain large  
307 amounts of glucosinolates, which are a nutritional source of thiocyanates and isothiocyanates.  
308 Those molecules can block the action of carcinogenic substances and suppress the expression  
309 of neoplasia in initiated cancer cells,<sup>53</sup> but they also act as goitrogens,<sup>13</sup> promoting thyroid  
310 tumour growth in rats.<sup>14,15</sup>

311 Strengths of the EPIC study are its prospective design, its large number of cancer cases, and  
312 the wide range of F&V and fruit juice intake across participants from 10 European countries  
313 with standardized information on diet and lifestyle exposures. Several limitations have to be  
314 taken into account. Although EPIC is a large study, participants are not representative of the  
315 whole population in most of the countries because of the criteria of recruitment, and therefore  
316 the results are not totally generalizable to general population. The measurement error in the  
317 estimation of F&V and fruit juice intake by dietary questionnaires may have attenuated our  
318 findings, although the use of the calibrated F&V and fruit juice data, obtained from the

319 standardized 24-HDR, did not alter the results. As discussed above, we do not have data on  
320 fruit juices and fruit nectars separately. Dietary and lifestyle habits during the follow-up  
321 period are not available in EPIC, although diet is relatively stable in adult populations through  
322 the years.

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

331

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542

**Supplementary table 1. Baseline characteristics of participants in the EPIC study according to quartiles of combined intake of vegetables and fruits**

Characteristics	Vegetables and fruits (g/d)			
	Q1	Q2	Q3	Q4
<b>Cutoffs (mg/d)</b>	<250	250-391	392-576	>576
<b>Sex, male (%)</b>	42	29.6	23.3	24.6
<b>Mean age (SD, y)</b>	50.3 (9.7)	51.2 (9.8)	51.7 (9.9)	51.7 (10.3)
<b>Mean BMI (SD, kg/m<sup>2</sup>)</b>	25.4 (4.1)	25.2 (4.1)	25.2 (4.3)	25.9 (4.6)
<b>Mean total energy (SD, kcal/d)</b>	1924 (609)	2024 (596)	2096 (596)	2257 (628)
<b>Mean alcohol (SD, g/d)</b>	13.9 (19.9)	12.3 (16.8)	11.3 (15.6)	10.4 (15.6)
<b>Smoking status (%)<sup>a</sup></b>				
Never	39.1	47.3	53.4	56.1
Former	26.9	28.2	26.7	24.9
Current	32.6	22.7	17.8	16.4
<b>Education (%)<sup>a</sup></b>				
Primary	30.4	27	28.3	34.3
Secondary	67.9	69.9	67.3	60.8
<b>Physical activity (%)<sup>a</sup></b>				
Inactive	51	51.3	55	58.4
Active	46.1	46.4	43.5	41
<b>Diabetes at baseline (%)<sup>a</sup></b>				
No	90.9	88.5	87.9	89.5
Yes	2.1	2.1	2.1	3.1
Unknown	7.2	9.2	9.1	7.1
<b>Menopausal status (%)<sup>a,b</sup></b>				
Premenopausal	38.3	34.7	33.2	33.9
Postmenopausal	39.2	42.7	44.5	45.4
Perimenopausal	20.6	20.1	19.3	17
Surgical menopause	2	2.6	3	3.8
<b>Oral contraceptive use (%)<sup>a,b</sup></b>				
No	31.6	35.7	41.4	50.2
Yes	63.6	61.6	56.7	48.5
Unknown	4.8	2.7	1.9	1.3
<b>Infertility problems (%)<sup>a,b</sup></b>				
No	44.5	56.5	69.1	79.3
Yes	1.5	2.6	3.7	4.3
Unknown	54	40.9	27.2	16.4

Abbreviations: BMI Body Mass Index; Q Quartile; SD Standard Deviation

<sup>a</sup>Missing values: Smoking status 9,676 (2.03%), Education 16,929 (3.56%), Physical activity 8,824 (1.85%), Oral contraceptive use 8,427 (1.77%), Infertility problems 111,162 (23.35%), Diabetes at baseline 38,970 (8.19%)

<sup>b</sup>% only in women (n=333,876)

**Supplementary table 2. Modelling strategy to estimate hazard ratios and 95% confidence intervals for differentiated thyroid cancer according to quartile of intake of vegetables, fruits and fruit juices in the EPIC study**

	Intake (g/d)	No of cases	Differentiated thyroid carcinoma				
			Model A1 <sup>a</sup>	Model A2 <sup>b</sup>	Model B1 <sup>c</sup>	Model B2 <sup>d</sup>	Model B3 <sup>3</sup>
			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<b>Total vegetables and fruits</b>							
Quartile 1	<250	137	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Quartile 2	250-391	163	0.93 (0.73-1.17)	0.93 (0.73-1.18)	0.93 (0.73-1.18)	0.91 (0.72-1.16)	0.90 (0.71-1.15)
Quartile 3	392-576	226	1.03 (0.81-1.30)	1.02 (0.81-1.30)	1.03 (0.81-1.31)	1.00 (0.78-1.27)	0.98 (0.77-1.25)
Quartile 4	>576	222	0.93 (0.73-1.20)	0.93 (0.72-1.19)	0.94 (0.73-1.22)	0.89 (0.68-1.15)	0.87 (0.67-1.13)
P-trend			0.69	0.64	0.78	0.44	0.38
Observed continuous (per 100g/d)			1.01 (0.97-1.04)	1.00 (0.97-1.04)	1.01 (0.98-0.99)	0.99 (0.97-1.03)	1.00 (0.97-1.03)
Calibrated continuous (per 100g/d)			1.03 (0.96-1.11)	1.03 (0.95-1.11)	1.03 (0.96-1.11)	1.01 (0.94-1.09)	1.09 (0.93-1.09)
<b>Vegetables</b>							
Quartile 1	<110	160	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Quartile 2	110-175	164	0.87 (0.69-1.09)	0.87 (0.69-1.09)	0.87 (0.70-1.09)	0.87 (0.69-1.08)	0.87 (0.69-1.09)
Quartile 3	176-276	204	0.93 (0.74-1.17)	0.93 (0.74-1.17)	0.94 (0.75-1.19)	0.93 (0.74-1.17)	0.93 (0.73-1.17)
Quartile 4	>276	220	0.91 (0.71-1.16)	0.90 (0.70-1.15)	0.92 (0.71-1.18)	0.89 (0.69-1.14)	0.87 (0.67-1.13)
P-trend			0.69	0.62	0.77	0.56	0.47
Observed continuous (per 100g/d)			0.99 (0.99-1.00)	0.98 (0.93-1.05)	0.99 (0.93-1.06)	0.98 (0.92-1.04)	0.97 (0.91-1.04)
Calibrated continuous (per 100g/d)			1.02 (0.84-1.24)	1.01 (0.83-1.23)	1.03 (0.84-1.25)	0.99 (0.81-1.21)	0.97 (0.79-1.19)
<b>Fruits</b>							
Quartile 1	<106	149	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Quartile 2	106-194	162	0.91 (0.73-1.15)	0.91 (0.72-1.15)	0.92 (0.73-1.15)	0.90 (0.71-1.13)	0.90 (0.71-1.13)
Quartile 3	195-314	194	0.90 (0.72-1.13)	0.90 (0.72-1.13)	0.91 (0.73-1.14)	0.88 (0.70-1.10)	0.88 (0.70-1.11)
Quartile 4	>314	243	1.04 (0.83-1.31)	1.04 (0.83-1.31)	1.06 (0.84-1.33)	1.00 (0.79-1.26)	1.01 (0.79-1.28)
P-trend			0.43	0.43	0.36	0.64	0.59
Observed continuous (per 100g/d)			1.02 (0.97-1.06)	1.02 (0.97-1.06)	1.02 (0.98-1.06)	1.00 (0.97-1.05)	1.01 (0.97-1.06)
Calibrated continuous (per 100g/d)			1.04 (0.95-1.13)	1.04 (0.95-1.13)	1.04 (0.95-1.14)	1.02 (0.93-1.12)	1.02 (0.93-1.12)
<b>Fruit juices</b>							
Quartile 1	<1	205	1(Ref)	1 (Ref)	1 (Ref)	1(Ref)	1 (ref)
Quartile 2	1-20	151	1.03 (0.82-1.29)	1.03 (0.82-1.30)	1.03 (0.82-1.29)	1.03 (0.82-1.29)	1.03 (0.82-1.30)
Quartile 3	21-94	207	1.14 (0.93-1.41)	1.16 (0.94-1.43)	1.15 (0.93-1.42)	1.16 (0.94-1.43)	1.17 (0.95-1.44)
Quartile 4	>94	185	1.19 (0.96-1.48)	1.22 (0.98-1.52)	1.21 (0.97-1.50)	1.23 (0.98-1.53)	1.24 (0.99-1.54)
P-trend			0.10	0.06	0.08	0.06	0.05
Observed continuous (per 100g/d)			1.02 (0.99-1.05)	1.02 (0.99-1.05)	1.02 (0.99-1.06)	1.02 (0.99-1.05)	1.02 (0.99-1.06)
Calibrated continuous (per 100g/d)			1.04 (0.95-1.14)	0.99 (0.92-1.08)	0.99 (0.92-1.08)	0.99 (0.92-1.08)	0.99 (0.92-1.08)

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

<sup>a</sup>Model A1: Cox model stratified by centre, age at baseline and sex

<sup>b</sup>Model A2: Model 1 additionally adjusted for BMI, smoking status, education, physical activity, menopausal status and type, oral contraceptive use, infertility problems

<sup>c</sup>Model B1 Cox model stratified by centre, age at baseline and sex, and adjusted for total energy intake

<sup>d</sup>Model B2: Model B1 additionally adjusted for BMI, smoking status, education, physical activity, menopause status and type, oral contraceptive use, infertility problems, and alcohol intake

<sup>c</sup>Model B3: Model B2 additionally adjusted for vegetables, fruits and/or fruit juices, accordingly.

**Supplementary table 3. Hazard ratios and 95% confidence intervals for overall, papillary and follicular thyroid cancer risk according to quartiles of intake of juices in separate analyses by physical activity status and categories of BMI in the EPIC study**

Intake	Overall differentiated TC				Papillary TC				FollicularTC			
	No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	P-value	No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	P-value	No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	P-value
<b>Physically inactive (n=256,627)</b>												
Quartile 1	<0.3	127	1 (ref)		104	1 (ref)	1 (ref)		18	1 (ref)	1 (ref)	
Quartile 2	0.3-16.4	92	1.05 (0.79-1.41)		71	1.01 (0.73-1.41)	1.01 (0.73-1.40)		16	1.23 (0.59-2.55)	1.27 (0.61-2.63)	
Quartile 3	16.5-78.6	117	1.17 (0.89-1.53)		94	1.16 (0.86-1.57)	1.16 (0.86-1.56)		17	1.30 (0.63-2.67)	1.39 (0.67-2.87)	
Quartile 4	>78.6	126	1.30 (0.99-1.71)		94	1.24 (0.91-1.68)	1.23 (0.90-1.67)		17	1.02 (0.48-2.18)	1.12 (0.51-2.42)	
P-trend			0.05			0.15	0.17			0.75	0.93	
Observed continuous (per 50g/d)			1.04 (1.00-1.08)	0.19 <sup>c</sup>		1.05 (1.00-1.09)	1.04 (1.00-1.09)	0.20 <sup>c</sup>		0.98 (0.87-1.10)	0.98 (0.87-1.10)	0.15 <sup>c</sup>
Calibrated continuous (per 50g/d)			1.03 (0.94-1.14)	0.20 <sup>c</sup>		1.06 (0.95-1.18)	1.06 (0.95-1.18)	0.14 <sup>c</sup>		0.95 (0.76-1.20)	0.95 (0.76-1.19)	0.58 <sup>c</sup>
<b>Physically active (n=210,657)</b>												
Quartile 1	<1.7	75	1 (ref)		64	1 (ref)	1 (ref)		7	1 (ref)	1 (ref)	
Quartile 2	1.7-28.6	66	0.98 (0.69-1.40)		57	1.00 (0.68-1.47)	0.99 (0.67-1.48)		9	1.45 (0.51-4.08)	1.52 (0.54-4.32)	
Quartile 3	28.7-100.1	76	1.07 (0.77-1.50)		63	1.04 (0.72-1.50)	0.78 (0.50-1.20)		10	1.58 (0.58-4.28)	1.64 (0.60-4.48)	
Quartile 4	>100.1	65	0.97 (0.69-1.39)		51	0.90 (0.61-1.32)	0.69 (0.45-1.08)		14	2.39 (0.91-6.28)	2.63 (0.98-7.02)	
P-trend			0.91			0.54	0.63			0.08	0.06	
Observed continuous (per 50g/d)			0.99 (0.94-1.05)			0.98 (0.91-1.05)	0.98 (0.91-1.05)			1.05 (0.96-1.15)	1.07 (0.97-1.19)	
Calibrated continuous (per 50g/d)			0.93 (0.80-1.08)			0.92 (0.77-1.10)	0.92 (0.77-1.09)			1.01 (0.80-1.27)	1.03 (0.81-1.31)	
<b>BMI&lt;25 (n=246,028)</b>												
Quartile 1	<1.2	108	1(ref)		93	1(ref)	1(ref)		8	1(ref)	1(ref)	
Quartile 2	1.2-27.6	78	0.92 (0.68-1.25)		63	0.86 (0.61-1.20)	0.87 (0.62-1.21)		14	1.98 (0.80-4.87)	1.95 (0.79-4.80)	
Quartile 3	27.7-100.1	95	1.11 (0.84-1.48)		81	1.11 (0.82-1.52)	1.14 (0.83-1.55)		11	1.48 (0.58-3.77)	1.46 (0.57-3.73)	
Quartile 4	>100.1	115	1.39 (1.05-1.84)		89	1.29 (0.95-1.76)	1.33 (0.98-1.82)		20	2.61 (1.09-6.23)	2.64 (1.09-6.38)	

P-trend			0.004	0.002		0.02	0.02		0.06	0.06	
Observed continuous (per 50g/d)			1.04 (1.00-1.09)	1.05 (1.00-1.09)	0.05 <sup>d</sup>	1.04 (1.00-1.08)	1.05 (1.00-1.10)	0.05 <sup>d</sup>	1.05 (0.95-1.15)	1.04 (0.95-1.15)	0.20 <sup>d</sup>
Calibrated continuous (per 50g/d)			1.00 (0.88-1.13)	1.00 (0.88-1.13)	0.87 <sup>d</sup>	0.99 (0.85-1.15)	0.99 (0.85-1.16)	0.78 <sup>d</sup>	1.05 (0.85-1.30)	1.04 (0.84-1.29)	0.46 <sup>d</sup>
<b>BMI<math>\geq</math>25 (n=230,079)</b>											
Quartile 1	<0.57	98	1(ref)	1(ref)	79	1(ref)	1(ref)	17	1(ref)	1(ref)	
Quartile 2	0.57-15.8	76	1.09 (0.78-1.52)	1.09 (0.78-1.52)	58	1.05 (0.72-1.54)	1.05 (0.72-1.54)	14	1.20 (0.55-2.61)	1.23 (0.56-2.68)	
Quartile 3	15.9-75.91	97	1.25 (0.91-1.71)	1.26 (0.91-1.73)	77	1.22 (0.86-1.74)	1.21 (0.85-1.73)	12	1.16 (0.52-2.61)	1.26 (0.56-2.86)	
Quartile 4	>75.91	81	1.04 (0.75-1.46)	1.06 (0.75-1.48)	61	0.98 (0.67-1.43)	0.96 (0.66-1.41)	13	0.98 (0.42-2.25)	1.10 (0.48-2.56)	
P-trend			0.93	0.99		0.71	0.64		0.76	0.98	
Observed continuous (per 50g/d)			0.99 (0.94-1.05)	0.99 (0.94-1.05)		0.99 (0.94-1.06)	0.99 (0.93-1.05)		0.98 (0.85-1.12)	0.99 (0.87-1.14)	
Calibrated continuous (per 50g/d)			0.99 (0.90-1.10)	0.99 (0.89-1.10)		1.02 (0.91-1.14)	1.01 (0.90-1.13)		0.91 (0.69-1.20)	0.93 (0.71-1.22)	

Abbreviations: BMI Body mass Index; HR Hazard Ratio; CI confidence interval; TC thyroid carcinoma

<sup>a</sup>Model A1: Cox model stratified by centre, age at baseline and sex

<sup>b</sup>Model B2: Cox model stratified by centre, age at baseline and sex, and adjusted for BMI, 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.

<sup>c</sup>p-heterogeneity for physically inactive vs. physically active using the Wald test

<sup>d</sup>p-heterogeneity for participants with a BMI<25 vs. participants with a BMI $\geq$ 25 using the Wald test

**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)
<b>WOMEN</b>										
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)
<b>MEN</b>										
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)

<b>ALL</b>	476,108	6,639,464	748	601	109	38	391 (250-576)	175 (110-276)	194 (106-314)	20(1-94)
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Abbreviations: NOS not otherwise specified

**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 <sup>c</sup>
		No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	No of cases	Model A1 <sup>a</sup> HR (95% CI)	Model B2 <sup>b</sup> HR (95% CI)	
<b>Total vegetables and fruits</b>											
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
<b>Vegetables</b>											
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
<b>Fruits</b>											
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
<b>Fruit juices</b>											
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

<sup>a</sup>Model A1: Cox model stratified by centre, age at baseline and sex,

<sup>b</sup>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.

<sup>c</sup>P for heterogeneity using the Wald test.

**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 <sup>d</sup>	
	Observed <sup>b</sup>	Calibrated <sup>c</sup>	Observed <sup>b</sup>	Calibrated <sup>c</sup>	Observed <sup>b</sup>	Calibrated <sup>c</sup>	Observed	Calibrated
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		
<b>Vegetables</b>								
Leafy vegetables (per 50g/d) <sup>a</sup>	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) <sup>e</sup>	0.56 (0.34-0.91) <sup>e</sup>	0.03	<0.001
<b>Fruits</b>								
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

<sup>a</sup>excluding Norway (n=33 972 participants)

<sup>b</sup>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.

<sup>c</sup>Model B2 applied to calibrated variables

<sup>d</sup>P for heterogeneity using the Wald test.

<sup>e</sup>After applying the Bonferroni correction, the inverse association was no longer statistically significant.