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Adapted Dietary Inflammatory Index and Differentiated Thyroid Carcinoma Risk in two French Population-Based Case-Control Studies

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Abstract

Purpose: Thyroid cancer is the most common endocrine cancer and its etiology is still not well understood. The aim of the present study was to assess the association between an adapted

dietary inflammatory index and differentiated thyroid cancer (DTC) risk in two population-based case-control studies (CATHY and YOUNG-THYR) conducted in France.

Methods: These studies included a total of 1321 DTC cases and 1502 controls, for which an adapted dietary inflammatory index (ADII) was computed based on food frequency questionnaires in each study separately. The association between ADII and thyroid cancer risk was assessed using logistic regression models controlling for potential confounders.

Results: Higher ADII scores, corresponding to a higher pro-inflammatory potential of the diet, were associated with higher DTC risk (odds ratio (OR) for 1 standard deviation (SD) increase: 1.09, 95% confidence interval (CI): 1.01, 1.18, P: 0.03). Associations were stronger in analyses restricted to women (OR for 1-SD increase: 1.14, 95% CI: 1.04, 1.25, P: 0.005), as well as in women with lower education level, current smoking, or high body mass index.

Conclusion: Our study suggests that a pro-inflammatory diet is associated with an increased risk of DTC, especially when combined with other inflammatory conditions such as tobacco smoking or overweight. Our findings will help better understand the role of diet-induced inflammation in DTC etiology.

Keywords:

Differentiated thyroid cancer; diet; inflammation; case-control study

Abbreviations:

ADII: Adapted dietary inflammatory index; BMI: Body mass index; CI: Confidence interval; CRP: C-reactive protein; DII: Dietary Inflammatory Index; DTC: Differentiated thyroid cancer; FFQ: Food Frequency Questionnaire; IL: Interleukin; ISD: Inflammatory Score of the Diet; OR: Odds ratio; SD: Standard deviation

Declarations

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Conflict of interest:

None declared

Availability of data and material:

The datasets used and/or analyzed during the current study are available from Thérèse Truong (therese.truong@inserm.fr) upon reasonable request

Code availability:

Not applicable

Authors' contributions:

The author's contribution were as follow – MCBR and TT coordinated the project. LL, NL, MCBR and TT designed and conducted the research; FDV, PG, CS, AVG, FBC, EA and TT were involved in the subject recruitment of CATHY and YOUNG-THYR studies. LL, VS, ECD, CX and MK performed the quality controls and data management of the datasets; MH and MP provided tables of food nutrients; LL performed the statistical analyses; NL, MCBR and TT supervised the statistical analyses; LL, NL, MCBR and TT drafted the manuscript. All authors reviewed the manuscript and approved the final version of the paper.

Ethics approval and consent to participate and for publication:

Participants from the CATHY and YOUNG-THYR studies provided written informed consent and each study was approved by their governing ethics committee.

1 INTRODUCTION

2 Thyroid cancer is the most common endocrine cancer, ranking ninth for incidence overall. It
3 represented 3% of all cancers worldwide and 5% of cancers in women in 2018 [1].

4 Differentiated thyroid cancers (DTC) account for more than 90% of all thyroid cancer
5 histological types. The incidence of thyroid cancer has been increasing worldwide since the
6 early 1980s. Part of this increase has been attributed to improvements in screening practices
7 leading to detection of microcarcinomas [2], but changes in environmental and lifestyle
8 exposures are also suspected to play a role [3]. The only well-established risk factor of DTC is
9 exposure to ionizing radiation, particularly during childhood [4]. Tall height and large body
10 size have also been consistently associated with risk of DTC [5–8]. Because DTC occurs
11 more frequently in women than in men, a role of hormonal and reproductive factors such as
12 menopausal status, use of oral contraceptives, age at menarche, and number of pregnancies
13 has been suggested [9, 10]. Previous papers that analyzed the role of dietary factors in thyroid
14 cancer mostly focused on foods that interfere with thyroid function, such as foods with high
15 iodine content[11], or vegetables containing goitrogenic substances[12], but the findings are
16 inconclusive. In the current study, we propose to further explore the role of dietary habits on
17 DTC risk by examining the inflammatory potential of the diet. Indeed, chronic inflammation
18 is known to play an important role in cancer initiation and progression.

19 Although thyroid cancer has been associated with inflammatory biomarkers [13, 14], the role
20 of chronic inflammation in thyroid cancer is still unclear. Several dietary factors are able to
21 modulate inflammatory biomarker levels and therefore have pro- or anti-inflammatory
22 properties [15, 16]. In this context, several scores have been developed in recent years to
23 quantify the level of diet-induced inflammation in an individual [17–20]. Only one previous
24 case-control study conducted in New Caledonia has investigated the association between this

25 type of score and thyroid cancer risk, and suggested that a pro-inflammatory diet is associated
26 with increased DTC risk [21]. The aim of the present study was to assess the association
27 between a dietary inflammatory index and DTC risk in a pooled analysis of two population-
28 based case-control studies conducted in metropolitan France.

29 MATERIALS AND METHODS

30 Study population

31 The CATHY study [9] was conducted in Calvados, Marne, and Ardennes, three French
32 counties covered by a cancer registry. All patients aged 25 years or older diagnosed with
33 papillary or follicular thyroid cancer between 2002 and 2007, and residing in these areas were
34 eligible. Controls reached by phone and who accepted to participate were assigned a year of
35 reference at random from 2002 to 2007, and were frequency-matched by 5-year age group and
36 study area with the cases in the corresponding year of diagnosis. To prevent possible selection
37 bias arising from differential participation rates across categories of socioeconomic status, the
38 control group was selected to reflect the distribution of the general population by
39 socioeconomic status categories. A total of 621 cases and 706 controls were included.

40 The YOUNG-THYR study [10] included patients younger than 35 years of age, diagnosed
41 with DTC between 2002 and 2006, and residing in regions of eastern France at the time of the
42 diagnosis (Alsace, Champagne-Ardenne, Nord-Pas-de-Calais, Ile-de-France, Corse, Franche-
43 Comté, Lorraine, Bourgogne, Languedoc-Roussillon, Rhône-Alpes, or Provence-Alpes-Côte
44 d'Azur). Cases were born after January 1st, 1971, thereby excluding those who were older
45 than 15 years of age at the time of the Chernobyl nuclear power plant accident. Controls were
46 selected from the general population and were individually matched to cases by sex, year of
47 birth, and region of residence during the year when the case was diagnosed with cancer. A
48 total of 805 cases and 876 controls were included.

49 Data collection

50 All participants from the CATHY and YOUNG-THYR studies provided informed written
51 consent prior to data collection.

52 In both studies, participants were interviewed face to face using a similar structured
53 questionnaire on education level, lifestyle factors, reproductive history, previous medical
54 conditions, anthropometric factors, and family history of thyroid cancer.

55 A food frequency questionnaire (FFQ), derived from a validated questionnaire especially
56 developed for a large French prospective cohort study [22], was used to assess the dietary
57 habits prior to the diagnosis for cases, or the year of reference for controls. However, the FFQ
58 differed slightly between the two studies. In the CATHY study, the FFQ included 158 items
59 covering major food groups consumed in France. In the YOUNG-THYR study, two
60 simplified FFQ were used, one regarding dietary habits during childhood and one during
61 adulthood. The latter, used in the present study, was limited to 64 items. In both studies,
62 portion size was determined using color photographs; mean daily micro- and macronutrient
63 intakes were calculated using the CIQUAL food composition database [23] and we
64 supplemented missing information with the NutriNet-Santé database [24].

65 Dietary inflammatory index computation

66 Computation of the index presented in the present study has been already detailed elsewhere
67 [25]. The index was computed in the CATHY study and the YOUNG-THYR study
68 separately. Briefly, we used the Adapted Dietary Inflammatory Index (ADII) proposed by van
69 Woudenberg et al [19] in combination with the updated dietary component inflammatory
70 weights proposed by Shivappa et al [18] instead of those proposed by Cavicchia et al [17].
71 These inflammatory weights are literature-derived and were assigned to a set of dietary
72 parameters according to their impact on a selection of inflammatory biomarkers (Interleukin

73 (IL)-1 β , IL-6, TNF α , C-reactive protein (CRP), IL-4 and IL-10). The weights used are
74 described in supplementary Table 1. Positive weights represent a pro-inflammatory effect
75 while negative weights represent an anti-inflammatory effect. For instance, positive weights
76 were assigned to saturated fat, protein, carbohydrates or cholesterol, while negative weights
77 were assigned to n-3 fatty acids or fibre. Out of the 40 possible dietary parameters, 31 were
78 available for the CATHY study and 29 for the YOUNG-THYR study. This ADII has been
79 proposed on the basis of nutritional rationale. First, the inflammatory weights of dietary
80 components are multiplied by the standardized energy-adjusted intake [26], which gives an
81 estimate of nutrient intake uncorrelated with total energy intake. Second, the ADII calculation
82 did not include alcoholic beverages (such as beer, wine, and liquor), total fat and energy, in
83 order to avoid including of their inflammatory effects in duplicate. Ethanol was included
84 instead of alcoholic beverages, and energy and total lipids were excluded because their
85 inflammatory effects were considered to be equivalent to the sum of the inflammatory effects
86 of all energy-providing macronutrients and all separate fatty acids, respectively. Finally, the
87 weight for ethanol was set to zero when the intake was >40g/day because the intake of ethanol
88 is not likely to be anti-inflammatory above this limit [27–29]. Positive values of ADII indicate
89 a pro-inflammatory diet and negative values correspond to an anti-inflammatory diet.

90 We also computed two other dietary inflammatory scores: the Dietary Inflammatory Index
91 (DII) developed by Shivappa et al. [18], and the Inflammatory Score of the Diet (ISD)
92 developed by Agudo et al. [20]. These scores differ in the way the total energy intake is taken
93 into account, the reference population used to standardize the dietary intakes, and the dietary
94 parameters included. The list of dietary components and the methods used for calculating the
95 dietary inflammatory scores are described in Supplementary Table 1. In this study, results
96 were quite similar for the three indexes. We chose to present the results of the ADII as main
97 results and those of the DII and ISD as supplementary results because of the nutritional

98 rationale detailed above, namely, (1) the use of standardized energy-adjusted intake instead of
99 raw intakes to reduce the between-person variation in dietary intake resulting from differences
100 in physical activity, body size, and metabolic efficiency, and (2) the exclusion of energy and
101 total lipids intakes as inflammatory parameters because it is likely that the inflammatory
102 effect of energy is the sum of the inflammatory effects of all energy-providing
103 macronutrients, and because it was assumed that the inflammatory effect of total fat is the
104 sum of the inflammatory effects of all separate fatty acids [19].

105 Statistical analyses

106 For both studies, we excluded participants who did not fill in the dietary questionnaires (n=68
107 and n=20, for the CATHY and YOUNG-THYR studies respectively), and those with missing
108 values on ADII parameters or covariates (n=23 and n=13, for the CATHY and YOUNG-
109 THYR studies respectively), those with extreme energy intakes below the 1st and above the
110 99th percentiles of the energy intake over energy requirement distribution in the population
111 (n=68 and n=33, for the CATHY and YOUNG-THYR studies respectively), leaving 554
112 cases and 654 controls for the CATHY study and 767 cases and 848 controls for the
113 YOUNG-THYR study. To describe the characteristics of the participants having a pro-
114 inflammatory or an anti-inflammatory profile in a representative sample, as well as the
115 nutrients and food the most consumed by those groups, we reported the distribution across
116 ADII quartiles among controls.

117 The ADII was analyzed both as a continuous (1-SD increase) and as a categorical variable
118 (quartiles based on ADII distribution in controls from each study separately) in a pooled
119 analysis of the two case-control studies, as well as in each study separately. Odds ratios (OR)
120 and corresponding 95% confidence intervals were calculated using multivariate unconditional
121 logistic regression. All models were adjusted for matching factors (age, sex, and area of
122 residence), the study (CATHY / YOUNG-THYR) and factors associated with DTC (family

123 history of thyroid cancer in first degree relatives, body mass index (BMI), education level,
124 smoking status, and self-declared ethnicity). Analyses restricted to women were additionally
125 adjusted for menopausal status, use of oral contraceptives, age at menarche, and number of
126 full-term pregnancies. Separate analyses were also conducted in papillary DTC only, and
127 according to the size of the carcinoma (≤ 10 mm and >10 mm). Assuming that
128 microcarcinomas are most likely detected during systematic screening, a stronger association
129 with microcarcinomas is expected while surveillance bias is acting fully. We did not conduct
130 separate analyses for men or follicular DTC as the sample sizes were too small for meaningful
131 analyses (see Table 1). In addition, stratified analyses were conducted in women by education
132 level, smoking status, and BMI. Potential interactions between the ADII and those variables
133 on DTC risk were tested using the likelihood ratio test, comparing models with and without
134 the interaction term. Test for trend were conducted by fitting models using a quantitative
135 variable equal to the median value of the exposure categories.

136 Finally, we conducted similar analyses using the two other scores (DII and ISD). Models were
137 further adjusted for alcohol-free energy intake since nutrient intakes were not adjusted for
138 energy intake, and subjects with higher overall food consumption tend to have higher dietary
139 scores but also higher energy intakes. The DII and ISD were strongly correlated (Pearson
140 coefficients >0.9 in both studies), while coefficients between ADII and DII or ISD ranged
141 from 0.56 to 0.68 (see Supplementary Table 2).

142 Statistical analyses were performed using SAS Enterprise Guide software (v7.1, Cary, NC)
143 and all tests were 2-sided.

144

145 RESULTS

146 Description of the study population

147 Characteristics of cases and controls of the pooled dataset are described in Table 1
148 (description by study is shown in Supplementary Table 3). Cases were more likely to be non-
149 European, to be less educated, to be non-current smokers, to have a higher BMI and energy
150 intake, to have a family history of thyroid cancer than controls, and also in women, they were
151 more likely to be postmenopausal, and ever users of oral contraceptives.

152 The mean ADII was -0.04 (SD, 3.65), ranging from -23.56 to 12.38 among controls, and 0.11
153 (SD, 3.70), ranging from -20.34 to 12.62 among cases. Characteristics of the controls
154 according to quartiles of ADII are presented in Supplementary Table 4. Subjects in the highest
155 ADII quartile were more likely to be of male gender, to be younger, to live in North of France,
156 to be European, to have lower BMI, and to have higher alcohol intake and alcohol-free energy
157 intake. Furthermore, participants in the highest ADII quartile were characterized by higher
158 intakes alcoholic drinks and cheese and yoghurt, while participants in the lowest ADII
159 quartile were characterized by higher intakes of eggs, cooked vegetables, fish and seafood,
160 salad and raw vegetables, and fruits. In terms of nutrients, participants in the highest ADII
161 quartile were characterized by higher intakes of ethanol, saturated fat, total lipids, and mono-
162 unsaturated fat, while participants in the lowest ADII quartile were characterized by higher
163 intakes of vitamins A, B6, B12, C, D, and E, magnesium, selenium, omega 3 fatty acids, folic
164 acid, dietary fibers, flavonoids and beta-carotene (see Supplementary Table 5).

165 ADII and DTC risk

166 Positive associations were found between the ADII and DTC risk in the total population (OR
167 for 1-SD increase: 1.09, 95% CI: 1.01, 1.18) and in women (OR for 1-SD increase: 1.14, 95%
168 CI: 1.04, 1.25) (see Table 2). Similar results were observed for papillary carcinomas (see
169 Table 2), and for the two other scores (the DII and the ISD, see Supplementary Table 7). The
170 positive associations were more striking for micro-carcinomas than for larger carcinomas in
171 women, and no association was found for larger carcinomas in general population (see Table

172 2), however, we the heterogeneity in the associations between micro- and larger carcinomas
173 was not significant. By analyzing the associations in the CATHY and YOUNG-THYR studies
174 separately, we found positive associations in the CATHY study and no associations in the
175 YOUNG-THYR study (see Supplementary Table 6).

176 Stratified analyses

177 ADII and DTC risk associations in women, stratified by education level, smoking status, and
178 BMI are shown in Table 3. Statistically significant associations between the ADII and DTC
179 risk were observed among women with lower education (OR for 1-SD increase: 1.33, 95%
180 CI: 1.15, 1.53), current smokers (OR for 1-SD increase: 1.32, 95% CI: 1.10, 1.59), and with
181 high BMI (OR for 1-SD increase: 1.24, 95% CI: 1.06, 1.44). No association was found for
182 women with higher education status, with BMI<25 and non-current smokers. The education
183 level was found to significantly modify the association between the ADII and DTC risk (p for
184 interaction: 0.007).

185 DISCUSSION

186 The present study, conducted in metropolitan France, showed positive associations between
187 pro-inflammatory dietary habits, as evidenced by higher ADII scores, and DTC risk. The
188 associations between ADII and DTC risk were more striking in women with lower education
189 level, that are current smokers, or in overweight.

190 The range of ADII in our study was similar to that reported in a French population of women
191 (from -24.6 to +13.4) [25]. The only other study that investigated associations between the
192 inflammatory potential of the diet and DTC risk was conducted in New Caledonia, a French
193 overseas territory, and found similar results, notably in ever smokers and obese individuals
194 [21]. So far, most studies that investigated the association between individual dietary factors
195 and DTC risk focused on factors that interfere with thyroid function. In our study, higher

196 intakes of fruit, vegetables, polyphenols, and omega 3 fatty acids were characteristic of a low
197 ADII score. In line with our results, previous prospective [30, 31] and case-control studies
198 [12, 32–34] found negative associations between these dietary factors and DTC risk (only in
199 overweight and obese individuals for polyphenols).

200 Intriguingly, in our study, participants in the highest quartile of ADII were characterized by a
201 higher consumption of ethanol and alcoholic beverages while the association between DTC
202 risk and alcohol intake is usually negative[35]. Of note, in the ADII computation, ethanol was
203 considered anti-inflammatory (weight=-0.278) when the intake was ≤ 40 g/day and has a null
204 weight otherwise. Indeed, alcohol has been shown to suppress the synthesis of pro-
205 inflammatory cytokines and chemokines [36, 37], but this anti-inflammatory effect was
206 reported only for moderate consumption [27–29]. However, moderate alcohol use has been
207 reported to have antioxidant properties through alcohol’s polyphenolic content [38], thus an
208 explanation for this apparent contradiction could be the type of alcoholic beverages consumed
209 (more or less rich in polyphenols). Moreover, alcohol intake may be associated with a less
210 healthy diet, characterized by higher consumption of saturated fat (considered as pro-
211 inflammatory in the ADII computation) and lower intakes of polyphenols, vitamins, omega 3
212 fatty acids, beta-carotene, and dietary fibre (considered as anti-inflammatory in the ADII
213 computation) which could offset anti-inflammatory properties of alcohol.

214 More broadly, a systematic review and meta-analysis on the association between the Dietary
215 Inflammatory Index and several cancers risk also showed positive associations between a pro-
216 inflammatory diet and several other cancers risk such as pancreas, colorectal, breast, prostate,
217 lung or bladder [39].

218 The correlation between DII/ISD and ADII is lower than expected but can be explained in
219 part by the way energy is taken into account: DII and ISD consider energy as an inflammatory
220 parameter since energy can act in itself as a pro-inflammatory factor through the increase in

221 adipose tissue [40], while the ADII do not consider energy as an inflammatory parameter but
222 use standardized energy-adjusted intake. Worthy of note is the importance of controlling for
223 energy intake in the development of such dietary indices [26]. Indeed, subjects with higher
224 overall food consumption tend to have higher intakes in all micronutrients –therefore higher
225 dietary scores – but also in energy intakes [40]; this results in a positive correlation between
226 energy intake and nutrient intake and in general, in a decrease of energy-unadjusted dietary
227 inflammatory scores (e.g., DII and ISD) when energy intake increases. Some differences in
228 the construction of these scores are also noted at the level of the reference population used to
229 standardize the dietary intakes, and the dietary parameters included. Although the correlation
230 between DII/ISD and ADII was not as strong as expected, the associations with DTC were
231 similar when DII and ISD were adjusted for energy in the models, thus, adjusting the intakes
232 for energy or adjusting in the model seems to have the same effect on the associations
233 between the scores and DTC.

234 In the present study, we also reported a more striking association between ADII and DTC risk
235 for microcarcinomas in women, and no association was found for larger carcinomas in
236 general population, suggesting that this association could be due to a potential surveillance
237 bias. However, this finding is not in accordance with our previous study on DTC risk [21]
238 where the association with DII was more pronounced in cases with larger carcinomas and
239 could also reflect a potential statistical artefact as the heterogeneity test was not significant.

240 We also observed an increased risk of DTC with higher ADII scores in women with lower
241 education level and in those who were current smokers. It is possible that women with lower
242 education level have a diet of poorer quality, e.g. including less antioxidants than women with
243 higher education. Indeed, participants with lower education level (primary or secondary) were
244 more likely to have higher ADII scores, while participants with higher education level (\geq
245 high-school degree) were more likely to have lower ADII scores (see Supplementary Table

246 4). Smoking was shown to have pro-oxidant properties [41] and is known to affect systemic
247 inflammation [42]. When combined with other conditions promoting inflammation, high
248 ADII diets may therefore increase the risk of DTC. In this study, we can note that although
249 current smoking was associated with lower DTC risk (see Table 1), the positive association
250 observed between high ADII and DTC risk was higher in current smokers than in never or
251 former smokers (as shown in Table 3).

252 Overall, our results are consistent with the hypothesis that diet plays a key role in the etiology
253 of DTC through, among others, inflammatory processes. On the one hand, certain dietary
254 factors used in ADII construction have a direct influence on several inflammatory parameters.
255 For instance, the nuclear factor- κ B pathway would be activated by saturated fatty acids, and
256 inhibited by polyphenols or omega-3 fatty acids [43] and diets high in carbohydrates and
257 saturated fats, and low in fibre would enhance innate immune responses by an increase of pro-
258 inflammatory cytokines and a decrease of anti-inflammatory cytokines [44]. Furthermore,
259 several dietary inflammatory indexes, including ADII, have been previously validated through
260 their association with several inflammatory biomarkers such as CRP, IL-6, or tumor necrosis
261 factor- α [45]. On the other hand, DTC risk has been positively associated with CRP [46], IL-6
262 [47, 48], IL-4 [46, 49], or IL-10 [13, 46, 47, 49]. However, the two latter interleukins are
263 considered as anti-inflammatory in dietary inflammatory indexes. This shows the limitation of
264 such indexes as they are not specific of any given disease, in this case, of thyroid cancer, and
265 can sometimes lead to inconsistencies. Several biological pathways support the role of
266 inflammation in DTC etiology. One of them is a perturbation of the microenvironment via
267 infiltration of the tumor by inflammatory cells, cytokines or chemokines [50]. Obesity seems
268 to play an important role in this process as the release of pro-inflammatory cytokines by the
269 adipose tissue is enhanced in obesity [21]. Plasma levels of IL-6 and high sensitive CRP and
270 adipose tissue gene expression of IL-6 and TNF- α have been shown to significantly increase

271 with BMI [51]. Furthermore, obesity and the associated metabolic pathologies are associated
272 with a chronic inflammatory response characterized by expanded emission of leptin, increased
273 acute-phase reactants, and activation of inflammatory signaling pathways [52]. Obese adipose
274 tissue is characterized by macrophage infiltration, leading to the production of reactive
275 oxygen species (ROS) [53–55]. This could explain the fact that we found a positive
276 association between risk of DTC and ADII among overweight women, which may suggest a
277 cumulative effect of these factors, leading to excessive inflammatory burden in the body [21].

278 The main strength of the present study pertained in the macroscopic approach of diet-related
279 inflammation which is allowed by the use of scores such as ADII. Indeed, in comparison to
280 studies that focused on single dietary factors, dietary inflammatory indexes take into account
281 the whole diet and potential synergistic or antagonist effects. In addition, our models were
282 adjusted on several risk factors as potential confounders. Some limitations also need to be
283 considered for this study. First, the simplified version of dietary questionnaire used for the
284 YOUNG-THYR study probably led to underestimate food intake of YOUNG-THYR's
285 participants, as we can see with the lower mean alcohol-free energy intake compared to
286 CATHY study (see Supplementary Table 3). We also observed a lower mean ADII in the
287 YOUNG-THYR study than in the CATHY study (see Supplementary Table 3), even at
288 similar ages (data not shown). This difference could be due to missing information in the
289 YOUNG-THYR study on some foods associated with a pro-inflammatory diet in the CATHY
290 study such as bread and refined grains that are highly consumed in France, as well as sweets
291 and confectionary, and cooking fats. The consequences of non-differential underestimation of
292 the inflammatory potential of the diet in the YOUNG-THYR study would result to bias the
293 OR towards the null value 1. However, in addition to the pooled analysis, we conducted
294 analyses separately in both studies and we did not report significant heterogeneity in the
295 associations between studies. Second, we cannot rule out memory and desirability bias,

296 inherent to retrospective studies. Nevertheless, both cases and controls were interviewed with
297 standardized questionnaires by trained interviewers and such bias would be non-differential,
298 and therefore would bias the association toward the null. In addition, the use of dietary
299 questionnaires derived from validated questionnaire, of color photographs to determine
300 portion size and the exclusion of participants with extreme energy intakes reduced these
301 biases. Finally, indexes are built from *a priori* hypotheses which are often not specific of one
302 research issue. The use of ADII in this study concerns the inflammatory potential of an
303 individual's diet but not particularly the inflammatory processes existing in DTC etiology.
304 The latter can be more specific, as with IL-4 and IL-10 biomarkers, considered as anti-
305 inflammatory in the ADII construction, but positively associated with DTC risk [13, 46, 47,
306 49]

307 In conclusion, our results showed that a high ADII score was associated with increased DTC
308 risk. Furthermore, this increased risk of DTC was especially pronounced among women with
309 lower education level, those who were smokers and overweight women. Our results need to
310 be confirmed in large-scale cohort studies and the use of inflammatory biomarkers in such
311 studies would help confirm the results. Our findings show the relevance of prevention
312 strategies of DTC towards diet-based approaches, all the more so that diet is a modifiable
313 factor.

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Table 1. Characteristics of Differentiated Thyroid Cancer Cases and Controls included in the pooled analyses of the CATHY study and the YOUNG-THYR study. The CATHY Study, France, 2002–2007 and the YOUNG-THYR Study, France, 2004-2006

Pooled study	Cases (N=1321)	Controls (N=1502)	OR^a	95% CI	P
Study					
CATHY	554 (41.9)	654 (43.5)			
YOUNG-THYR	767 (58.1)	848 (56.5)			
Age (years)					
Continuous	37.3±15	36.9±15			
< 20	72 (5.5)	76 (5.1)			
20 - 29	430 (32.6)	504 (33.6)			
30 - 39	365 (27.6)	429 (28.6)			
40 - 49	127 (9.6)	159 (10.6)			
50 - 59	188 (14.2)	177 (11.8)			
60 - 69	96 (7.3)	98 (6.5)			
≥ 70	43 (3.3)	59 (3.9)			
Sex					
Men	284 (21.5)	381 (25.4)			
Women	1037 (78.5)	1121 (74.6)			
Residence area					
North ^b	601 (45.5)	658 (43.8)			
South ^c	553 (41.9)	614 (40.9)			
West ^d	167 (12.6)	230 (15.3)			
Ethnicity					
European	1187 (89.86)	1429 (95.14)	1	Referent	
African/Caribbean	70 (5.3)	26 (1.73)	3.34	2.11, 5.3	<0.0001
Other	64 (4.84)	47 (3.13)	1.69	1.15, 2.49	0.008
Education					
Primary	191 (14.46)	166 (11.05)	1.58	1.22, 2.05	0.0005
Secondary	399 (30.2)	379 (25.23)	1.44	1.21, 1.72	<0.0001
High-school degree and higher	731 (55.34)	957 (63.72)	1	Referent	
Smoking status					
Never	704 (53.29)	736 (49)	1	Referent	
Former	283 (21.42)	289 (19.24)	1.06	0.87, 1.29	0.6
Current	334 (25.28)	477 (31.76)	0.74	0.62, 0.88	0.0007
BMI (kg/m ²)					
Continuous	24.6±5.2	24.0±4.9	1.13	1.05, 1.22	0.002
< 25	818 (61.92)	1001 (66.64)	1	Referent	
[25 - 30[322 (24.38)	344 (22.9)	1.18	0.98, 1.42	0.08
≥ 30	181 (13.7)	157 (10.45)	1.41	1.11, 1.8	0.004
				P-trend	0.002
Family history of thyroid cancer					
No	1256 (95.08)	1464 (97.47)	1	Referent	
Yes	65 (4.92)	38 (2.53)	2.04	1.35, 3.07	0.0006
Alcohol intake (g/d)					
Continuous	4.4±11.0	5.5±13.5	0.93	0.85, 1.01	0.1
Alcohol-free energy intake (kcal/d)					
Continuous	1801.7±827.6	1770.9±824.8	1.11	1.02, 1.21	0.02
Histological type of carcinoma					
Papillary	1187 (89.86)				

Follicular	134 (10.14)				
Carcinoma size (papillary only)					
≤10mm	398 (33.59)				
>10mm	787 (66.41)				
Missing	2				
Women	Cases (N=1008)	Controls (N=1098)	OR^e	95% CI	P
Age at menarche (years)					
Continuous	12.7±1.6	12.8±1.5	0.96	0.88, 1.04	0.3
≤ 11	220 (21.83)	204 (18.58)	1.23	0.96, 1.59	0.1
12	248 (24.6)	297 (27.05)	0.95	0.75, 1.21	0.7
13	254 (25.2)	286 (26.05)	1	Referent	
14	160 (15.87)	179 (16.3)	0.99	0.76, 1.31	1.0
≥ 15	126 (12.5)	132 (12.02)	1.04	0.77, 1.41	0.8
				P-trend	0.3
Menopausal status					
Premenopausal	759 (75.3)	891 (81.15)	1	Referent	
Postmenopausal (natural)	217 (21.53)	189 (17.21)	1.77	1.21, 2.59	0.003
Postmenopausal (artificial)	32 (3.17)	18 (1.64)	2.71	1.38, 5.32	0.004
Number of full-term pregnancy					
0	340 (33.73)	410 (37.34)	1	Referent	
1	209 (20.73)	237 (21.58)	1.05	0.82, 1.35	0.7
2	266 (26.39)	278 (25.32)	1.14	0.89, 1.47	0.3
≥3	193 (19.15)	173 (15.76)	1.33	0.97, 1.81	0.08
				P-trend	0.08
Oral contraceptives					
Never	239 (23.71)	192 (17.49)	1	Referent	
Former	483 (47.92)	539 (49.09)	0.74	0.59, 0.93	0.01
Current	286 (28.37)	367 (33.42)	0.64	0.5, 0.83	0.0007

Data are N (%) for categorical variables

Data are mean (SD) for continuous variables

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; OR, Odds Ratio; SD, Standard Deviation

^a Logistic regression adjusted for age, sex, residence area

^b Alsace, Champagne-Ardennes, Nord-Pas-de-Calais, Ile-de-France, Franche-Comté, Lorraine, Bourgogne

^c Rhône-Alpes, Provence-Alpes-Côte d'Azur, Corse, Languedoc-Roussillon

^d Basse-Normandie

^e Logistic regression adjusted for age, residence area

Table 2. Associations Between Risk of Differentiated Thyroid Cancer and ADII, Considering All Histological Subtypes or the Papillary Subtype Only and According to the Size of Carcinoma. The CATHY Study, France, 2002–2007 and the YOUNG-THYR Study, France, 2004-2006

	Cases / Controls	Overall			Carcinoma size								P-heterogeneity
		OR	95% CI	P	≤ 10 mm				> 10 mm				
					Cases / Controls	OR	95% CI	P	Cases / Controls	OR	95% CI	P	
Total sample ^a													
For 1-SD increase	1321 / 1502	1.09	1.01, 1.18	0.03	404 / 1502	1.18	1.05, 1.33	0.008	914 / 1502	1.05	0.96, 1.15	0.3	0.7
Quartile 1	300 / 374	1	Referent		81 / 374	1	Referent		218 / 374	1	Referent		
Quartile 2	333 / 377	1.16	0.93, 1.44		117 / 377	1.53	1.09, 2.15		216 / 377	1.02	0.80, 1.30		
Quartile 3	350 / 376	1.24	1.00, 1.55		98 / 376	1.31	0.92, 1.85		251 / 376	1.22	0.96, 1.55		
Quartile 4	338 / 375	1.26	1.01, 1.57		108 / 375	1.56	1.10, 2.20		229 / 375	1.16	0.91, 1.48		
			P-trend	0.03			P-trend	0.03			P-trend	0.1	
In women ^b													
For 1-SD increase	1008 / 1098	1.14	1.04, 1.25	0.005	316 / 1098	1.20	1.05, 1.38	0.01	690 / 1098	1.11	1.00, 1.23	0.047	0.8
Quartile 1	221 / 272	1	Referent		60 / 272	1	Referent		160 / 272	1	Referent		
Quartile 2	265 / 280	1.23	0.95, 1.59		89 / 280	1.51	1.01, 2.24		176 / 280	1.13	0.85, 1.50		
Quartile 3	249 / 276	1.20	0.92, 1.54		81 / 276	1.41	0.95, 2.11		168 / 276	1.11	0.83, 1.48		
Quartile 4	273 / 270	1.37	1.06, 1.77		86 / 270	1.55	1.04, 2.30		186 / 270	1.31	0.98, 1.74		
			P-trend	0.02			P-trend	0.04			P-trend	0.09	
Papillary cancer cases only in women ^b													
For 1-SD increase	918 / 1098	1.14	1.03, 1.25	0.007	312 / 1098	1.21	1.05, 1.39	0.009	605 / 1098	1.10	0.99, 1.22	0.08	0.8
Quartile 1	197 / 272	1	Referent		59 / 272	1	Referent		137 / 272	1	Referent		
Quartile 2	245 / 280	1.27	0.98, 1.65		87 / 280	1.50	1.00, 2.23		158 / 280	1.19	0.88, 1.60		
Quartile 3	232 / 276	1.24	0.96, 1.62		81 / 276	1.43	0.96, 2.14		151 / 276	1.15	0.86, 1.56		
Quartile 4	244 / 270	1.37	1.05, 1.78		85 / 270	1.55	1.04, 2.31		159 / 270	1.29	0.96, 1.74		
			P-trend	0.03			P-trend	0.04			P-trend	0.1	

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; SD, Standard Deviation

^a Logistic regression adjusted for age, sex, residence area, study, ethnicity, family history of thyroid cancer, BMI, education level, smoking status

^b Logistic regression adjusted for age, residence area, study, ethnicity, family history of thyroid cancer, BMI, education level, smoking status, menopausal status, oral contraceptives, age at menarche, and number of full-term pregnancies

Table 3. Associations Between Risk of Differentiated Thyroid Cancer and ADII in Women, Stratified by Education Level, Smoking Status and BMI. The CATHY Study, France, 2002–2007 and the YOUNG-THYR Study, France, 2004–2006

	Cases (%)	Controls (%)	OR	95% CI	P	P-interaction ^a
Education						0.007
Primary / secondary ^b						
For 1-SD increase	450	372	1.33	1.15, 1.53	0.0001	
Quartile 1	80 (17.78)	87 (23.39)	1	Referent		
Quartile 2	113 (25.11)	98 (26.34)	1.31	0.85, 2.01		
Quartile 3	118 (26.22)	92 (24.73)	1.51	0.98, 2.33		
Quartile 4	139 (30.89)	95 (25.54)	1.77	1.16, 2.70		
				P-trend	0.006	
High-school degree and higher ^b						
For 1-SD increase	558	726	1.01	0.90, 1.14	0.8	
Quartile 1	141 (25.27)	185 (25.48)	1	Referent		
Quartile 2	152 (27.24)	182 (25.07)	1.20	0.87, 1.65		
Quartile 3	131 (23.48)	184 (25.34)	1.02	0.73, 1.41		
Quartile 4	134 (24.01)	175 (24.1)	1.15	0.83, 1.60		
				P-trend	0.6	
Smoking status						0.1
Never / former ^c						
For 1-SD increase	751	761	1.08	0.97, 1.20	0.2	
Quartile 1	177 (23.57)	194 (25.49)	1	Referent		
Quartile 2	194 (25.83)	201 (26.41)	1.08	0.81, 1.45		
Quartile 3	190 (25.3)	192 (25.23)	1.13	0.84, 1.52		
Quartile 4	190 (25.3)	174 (22.86)	1.25	0.92, 1.69		
				P-trend	0.1	
Current ^c						
For 1-SD increase	257	337	1.32	1.10, 1.59	0.003	
Quartile 1	44 (17.12)	78 (23.15)	1	Referent		
Quartile 2	71 (27.63)	79 (23.44)	1.70	1.00, 2.89		
Quartile 3	59 (22.96)	84 (24.93)	1.47	0.86, 2.54		
Quartile 4	83 (32.3)	96 (28.49)	1.74	1.03, 2.92		
				P-trend	0.07	
BMI (kg/m ²)						0.2
< 25 ^d						
For 1-SD increase	638	774	1.09	0.97, 1.22	0.1	
Quartile 1	137 (21.47)	171 (22.09)	1	Referent		
Quartile 2	171 (26.8)	205 (26.49)	1.13	0.82, 1.55		
Quartile 3	157 (24.61)	202 (26.1)	1.05	0.76, 1.45		
Quartile 4	173 (27.12)	196 (25.32)	1.22	0.89, 1.68		
				P-trend	0.3	
≥ 25 ^d						
For 1-SD increase	370	324	1.24	1.06, 1.44	0.006	
Quartile 1	84 (22.7)	101 (31.17)	1	Referent		
Quartile 2	94 (25.41)	75 (23.15)	1.54	0.98, 2.41		
Quartile 3	92 (24.86)	74 (22.84)	1.61	1.03, 2.52		
Quartile 4	100 (27.03)	74 (22.84)	1.77	1.14, 2.77		
				P-trend	0.01	

Abbreviations: ADII, Adapted Dietary Inflammatory Index; BMI, Body Mass Index; CI, Confidence Interval; OR, Odds Ratio; SD, Standard Deviation

^a P-value for interaction between the continuous ADII and the corresponding variable for the model adjusted for age, residence area, study, ethnicity, family history of thyroid cancer, BMI, education level, smoking status, menopausal status, oral contraceptives, age at menarche, and number of full-term pregnancies

^b Logistic regression adjusted for age, residence area, study, ethnicity, family history of thyroid cancer, BMI, smoking status, menopausal status, oral contraceptives, age at menarche, and number of full-term pregnancies

^c Logistic regression adjusted for age, residence area, study, ethnicity, family history of thyroid cancer, BMI, education level, menopausal status, oral contraceptives, age at menarche, and number of full-term pregnancies

^d Logistic regression adjusted for age, sex, residence area, study, ethnicity, family history of thyroid cancer, education level, smoking status, menopausal status, oral contraceptives, age at menarche, and number of full-term pregnancies

Supplementary materials

Supplementary Table 1: Dietary components and the methods used for calculation of the dietary inflammatory scores

Supplementary Table 2: Pearson correlation matrix of the dietary inflammatory scores.

Supplementary Table 3: Characteristics of Differentiated Thyroid Cancer Cases and Controls included in the analyses.

Supplementary Table 4: Characteristics of Controls Across Quartiles of ADII.

Supplementary Table 5: Nutritional Intakes of Controls Across Quartiles of ADII.

Supplementary Table 6: Associations Between Risk of Differentiated Thyroid Cancer and ADII in the CATHY and the YOUNG-THYR studies.

Supplementary Table 7: Risk of Differentiated Thyroid Cancer According to Quartile Groups of scores.