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Dietary intake of total polyphenol and polyphenol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort

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The entire manuscript is 4,120 words (including abstract (242 words), text (3,878 words), 45 references, 3 tables, 1 figure and 2 supplementary tables).

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RUNNING TITTLE: Polyphenols and colorectal cancer in EPIC

KEY WORDS: Polyphenols, intake, diet, colorectal cancer, prospective cohort, EPIC

LIST OF ABBREVIATIONS: BMI, body mass index; CRC, colorectal cancer; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; ICD, International Classification of Diseases; NOS, not otherwise specified; SD, standard deviation.

1 **ABSTRACT**

2 Polyphenols may play a chemopreventive role in colorectal cancer (CRC);
3 however, epidemiological evidence supporting a role for intake of individual
4 polyphenol classes, other than flavonoids is insufficient. We evaluated the
5 association between dietary intakes of total and individual classes and
6 subclasses of polyphenols and CRC risk and its main subsites, colon and
7 rectum, within the European Prospective Investigation into Cancer and Nutrition
8 (EPIC) study. The cohort included 476,160 men and women from 10 European
9 countries. During a mean follow-up of 14 years, there were 5,991 incident CRC
10 cases, of which 3,897 were in the colon and 2,094 were in the rectum.
11 Polyphenol intake was estimated using validated centre/country specific dietary
12 questionnaires and the Phenol-Explorer database. In multivariable-adjusted Cox
13 regression models, a doubling in total dietary polyphenol intake was not
14 associated with CRC risk in women ($HR_{\log 2} = 1.06$, 95 % CI 0.99-1.14) or in
15 men ($HR_{\log 2} = 0.97$, 95 % CI 0.90-1.05), respectively. Phenolic acid intake,
16 highly correlated with coffee consumption, was inversely associated with colon
17 cancer in men ($HR_{\log 2} = 0.91$, 95 % CI 0.85-0.97) and positively associated with
18 rectal cancer in women ($HR_{\log 2} = 1.10$, 95 % CI 1.02-1.19); although
19 associations did not exceed the Bonferroni threshold for significance. Intake of
20 other polyphenol classes was not related to colorectal, colon or rectal cancer
21 risks. Our study suggests a possible inverse association between phenolic acid
22 intake and colon cancer risk in men and positive with rectal cancer risk in
23 women.

24

25 INTRODUCTION

26 Colorectal cancer (CRC) is the third most common cancer and the fourth most
27 common cause of death from cancer worldwide, with 1.4 million new cases and
28 694,000 deaths in 2012 (1). Lifestyle (physical inactivity, body fatness, tobacco
29 smoking and alcohol consumption) and dietary factors, such as a high intake of
30 red and processed meat and low intake of fruit and vegetables, are known to
31 increase CRC risk (2).

32 Polyphenols are bioactive compounds naturally contained in plant-based foods,
33 such as tea, coffee, wine, fruit, vegetables, whole-grain cereals, and cocoa (3).
34 Experimental studies have shown anti-carcinogenic properties of polyphenols
35 against CRC through several plausible biological mechanisms including
36 modulation of nuclear factor (NF)- κ B genes involved in inflammation and
37 carcinogenesis, reduction of oxidative damage to lipids and DNA, induction of
38 phase I and II enzymes, inhibition of angiogenesis, stimulation of DNA repair
39 and apoptosis (4-7). Based on their chemical backbone, polyphenols are
40 divided into 4 main classes: flavonoids, phenolic acids, lignans, and stilbenes
41 (3). Polyphenols can be absorbed in the small intestine, although the vast
42 majority, from 50 to 99% depending on the polyphenol, transit down to the colon
43 where they can be metabolized by the gut microbiota and partially absorbed in
44 the con as small phenolic acids (8). Furthermore, polyphenols can modulate gut
45 microbiota, both in quantity and type of species (9). Imbalanced gut microbiota,
46 called dysbiosis, can alter both metabolism and absorption of polyphenols, and
47 may also induce aberrant molecular signalling, triggering the CRC pathogenesis
48 (10).

49 To date, several case-control studies suggest an inverse association between
50 flavonoid and lignan intake and CRC risk (3). However, no association in cohort
51 studies has been observed so far (3;11;12) including our previous results in the
52 European Prospective Investigation into Cancer and Nutrition (EPIC) study with
53 a shorter follow-up (13); except for the Iowa Women's Health study, in which an
54 inverse association between flavanol intake and rectal cancer risk was shown
55 (14). To our knowledge, there is only one case-control study investigating the
56 relationships with other polyphenol classes, such as phenolic acids, stilbenes
57 and other minor subclasses in Japan (15). In this previous study, intakes of
58 coffee polyphenols and consequently coffee consumption were inversely
59 associated with CRC risk in men and women, especially with colon cancer (15).

60 The Phenol-Explorer (www.phenol-explorer.eu) (16), a food composition
61 database on all known dietary polyphenols, greatly facilitates the assessment of
62 relationships between polyphenol intake and chronic disease risk. The aim of
63 the present study was to investigate the associations between the intake of total
64 polyphenols and individual polyphenol subclasses and CRC risk and by subsite
65 (colon and rectum) in the EPIC study, a large cohort with a high variability in
66 polyphenol intake and a long follow-up (17).

67 **MATERIALS AND METHODS**

68 **Subjects and study design**

69 EPIC is an on-going cohort consisting of 521,324 adult participants, mostly
70 recruited from the general population, enrolled between 1992 and 2000 from 23
71 centres in 10 European countries: Denmark, France, Germany, Greece, Italy,

72 the Netherlands, Norway, Spain, Sweden and the United Kingdom (18). All
73 participants gave written informed consent, and the study was approved by the
74 local ethics committees in the participating countries and the ethical review
75 board of the International Agency for Research on Cancer (IARC). We excluded
76 participants with prevalent cancer other than non-melanoma skin cancer at
77 baseline or with missing information on date of diagnosis or incomplete follow-
78 up data (n=29,332), missing data on dietary or lifestyle factors (n=6,259),
79 extreme energy intake and/or expenditure (participant in the top or the bottom
80 1% of the distribution of the ratio of total energy intake to energy requirement;
81 n=9,573). In the current analysis, 476,160 men and women were included.

82 **Identification and follow-up of colorectal cancer cases**

83 Cancer cases were identified through population cancer registries in Denmark,
84 Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. In
85 France, Germany, Greece and Naples-Italy, a combination of methods was
86 used including health insurance records, cancer and pathology registries, and
87 by active follow-up of study participants and their next of kin. Vital status was
88 collected from regional or national mortality registries.

89 Cancer incidence data were coded according to the 10th revision of the
90 International Statistical Classification of Diseases, Injuries and Causes of Death
91 (ICD-10) and the second revision of the International Classification of Diseases
92 for Oncology (ICDO-2). Proximal colon cancers included those within the
93 cecum, appendix, ascending colon, hepatic flexure, transverse colon, and
94 splenic flexure (C18.0–18.5). Distal colon cancers included those within the
95 descending (C18.6) and sigmoid (C18.7) colon. Overlapping (C18.8) and

96 unspecified (C18.9) lesions of the colon were grouped among all colon cancers
97 only (C18.0-C18.9). Cancer of the rectum included tumours occurring at the
98 recto sigmoid junction (C19) and rectum (C20). Five hundred and fourteen
99 cases were censored because they were carcinoma in situ (n=193), non-
100 adenocarcinoma, mixed types or not well defined (n=312), unknown histology of
101 the cancer (n=5), or a CRC originating from other organs (n=4).

102 **Dietary assessment and data collection**

103 At recruitment, validated country/centre-specific dietary questionnaires were
104 used for recording habitual diet over the previous 12 months (18;19). Most
105 centres utilized a self-administered food frequency questionnaire. In the
106 remaining centres (Greece, Spain, and Ragusa and Naples-Italy), a face-to-face
107 diet history questionnaire was employed to collect dietary information. In
108 Malmö-Sweden, a method combining a food frequency questionnaire with a 7-
109 day dietary diary and 1h interview was used. Total energy, alcohol, and nutrient
110 intakes were estimated by using the standardized EPIC Nutrient Database (20).

111 Lifestyle questionnaires were collected to obtain information on lifetime and
112 smoking status, physical activity classified according to the Cambridge Physical
113 Activity Index (21), education, menstrual and reproductive history. Height and
114 weight were measured at baseline in all centres except for Norway, France, and
115 the majority of participants in EPIC-Oxford where anthropometric measures
116 were self-reported (18).

117 **Polyphenol intake**

118 Dietary polyphenol intake was estimated using the Phenol-Explorer database
119 (16) accounting for cooking and processing of foods via retention factors (22),
120 as previously described (17;23). Total polyphenols was calculated as the sum of
121 all classes of polyphenols: flavonoids [anthocyanidins, chalcones,
122 dihydrochalcones, dihydroflavonols, flavanols (including flavan-3-ol monomers,
123 proanthocyanidins, theaflavins), flavanones, flavones, flavonols, and
124 isoflavones], phenolic acids (hydroxybenzoic acids, hydroxycinnamic acids, and
125 hydroxyphenylacetic acids), lignans, stilbenes, and other minor polyphenols
126 (alkylphenols, tyrosols, alkylmethoxyphenols, furanocoumarins,
127 hydroxybenzaldehydes, and hydroxycoumarins). The content of polyphenols
128 was expressed in mg/100 g of food fresh weight.

129 **Statistical analysis**

130 Polyphenol intakes were analysed as categorical variables based on quintiles of
131 the distribution among the entire EPIC cohort and by sex. Tests for linear trend
132 were performed by assigning the medians of each quintile as scores.
133 Polyphenol intakes were also analysed as continuous variables, after log₂
134 transformation to improve normality of intake distributions. Each increase of one
135 unit corresponded to a doubling in intake.

136 Multivariable Cox proportional hazard models were used to calculate hazard
137 ratios (HR) and 95% confidence intervals (CIs) of the associations between
138 total, classes and subclasses of polyphenol intakes and CRC risk. A chi-
139 squared test based upon the scaled Schoenfeld residuals was used to ensure
140 that the assumptions of proportional hazards were met. Age was the primary
141 time variable in all models. Entry time was age at recruitment and exit time was

142 age at diagnosis, death or censoring date (lost or end of follow-up), whichever
143 came first. Model 1 was stratified by centre (to control for differences in
144 questionnaires, follow-up procedures) and age at baseline (1-y interval). Model
145 2 was additionally adjusted for non-dietary variables: smoking status and
146 intensity (never, former quit <11 years, former quit 11–20 years, former quit >20
147 years, current <16 cigarettes/d, current 16–25 cigarettes/d, current >25
148 cigarettes/d, current occasional, and not specified), physical activity (inactive,
149 moderately inactive, moderately active, active, and not specified), education
150 level (none, primary school, technical/professional school, secondary school,
151 university or higher, and not specified), and body mass index (BMI, continuous
152 kg/m²); and in women also for menopausal status (pre-, peri-, post-menopausal,
153 surgical menopause), hormone replacement therapy use (yes, no, and
154 unknown), and oral contraceptive use (yes, no, and unknown). Model 3 was
155 further adjusted for dietary variables: total energy intake (kJ/d), alcohol (g/d),
156 red and processed meat (g/d), fibre (g/d) and calcium (mg/d) intakes. The
157 multivariable model for phenolic acids was additionally adjusted for coffee
158 intake, because coffee is its main food source by far (17). Moreover, model 1
159 and 2 were also adjusted for total energy intake to assess the effect of absolute
160 versus relative intakes of polyphenols in the diet. Results of Cox models with
161 and without adjusting for total energy intake were almost identical. Furthermore,
162 polyphenol intakes were also included in the statistical models as nutrient
163 density (mg/8240kJ day) (24). This energy-adjustment method did not modify
164 the results appreciably.

165 Interactions between polyphenol intakes (continuous as mg/day) and sex, age
166 (<55 years, 55 to 65 years, or >65 years), BMI (BMI<25, 25 to <30, ≥30 kg/m²),

167 tobacco smoking status (never, former, current smokers) and alcohol
168 consumption (for women <15g/d and ≥15g/d; and for men <30g/d and ≥30g/d)
169 were evaluated in separate analyses. The statistical significance of interactions
170 on the multiplicative scale was assessed using the likelihood ratio test.
171 Separate sex-specific models were fitted because a statistically significant
172 interaction between sex and intake of total polyphenols was detected. In
173 addition, we assessed separate models by smoking status category because a
174 statistically significant interaction with smoking status (never, former, and
175 current smokers) was observed. The Wald test statistic was used to evaluate
176 heterogeneity by anatomical subsites of CRC (colon, proximal colon, distal
177 colon, and rectum). Additional analyses by length of follow-up [censoring data at
178 3-, 6-, 9-, 12-, 15-, 18-years, and maximum of follow-up (22.8 years)] were
179 performed. Sensitivity analyses were performed by repeating main analyses
180 after the exclusion of 462 CRC cases diagnosed during the first 2 years of
181 follow-up (279 colon and 183 rectum cancer cases). All P values presented are
182 2-tailed and were considered to be statistically significant when $P < 0.05$. To
183 account for multiple testing for the subclasses of polyphenols, Bonferroni
184 correction was used and then results were considered statistically significant if
185 $P < 0.05/26$ (number of tests for the intakes of all polyphenol subclasses) < 0.002 .
186 All statistical analyses were conducted using R 3.2.1 software (R Foundation for
187 Statistical Computing, Vienna, Austria).

188 **RESULTS**

189 During 13.9 (4.0) years of mean (SD) follow-up, 5,991 (56.8% in women)
190 incident primary CRC cases were diagnosed, of which 3,897 were identified as
191 colon cancers (including 1,877 proximal, 1,743 distal, and 277 overlapping or

192 unspecified colon cancers) and 2,094 as rectum cancers. The number of
193 participants and distribution of CRC cases by country and sex are presented in
194 **Table 1**. The highest estimated median of total polyphenol intakes among both
195 sexes were in Denmark; whereas the lowest intakes amongst women and men
196 were observed in Norway and Spain, respectively (Table 1). Phenolic acids
197 were the main contributors to total polyphenols (51.0%), followed by flavonoids
198 (44.2%), other minor polyphenol classes (4.4%), lignans (0.2%) and stilbenes
199 (0.2%). Baseline characteristics of study participants by quintile of total
200 polyphenol intake are shown in **Supplementary Table 1**. Men and women in
201 the higher polyphenol intake groups were older, more physically active, had a
202 lower BMI, higher educational level, and had a lower proportion of never
203 smokers. Higher total polyphenol intake was also associated with higher
204 average intakes of total energy, alcohol, calcium, fibre and red meat compared
205 to participants with lower total polyphenol intakes. Furthermore, women with
206 higher total polyphenol intakes were more likely to be post-menopausal and
207 users of hormone replacement therapy and oral contraceptives than those with
208 lower total polyphenol intakes.

209 In multivariable models, total polyphenol intake was not associated with CRC
210 risk in either women ($HR_{\log 2} = 1.06$, 95 % CI 0.99 - 1.14) or men ($HR_{\log 2} = 0.97$,
211 95 % CI 0.90 - 1.05) ($P_{\text{sex-interaction}} < 0.001$) (**Table 2**). Null associations were
212 also observed with the risk of colon cancer and its anatomical subsites
213 (proximal and distal) in women; although a borderline statistically significant
214 inverse association was observed in men for colon cancer, especially for
215 proximal cancer ($HR_{\log 2} = 0.85$, 95 % CI 0.73 – 0.99). Higher intakes of total
216 polyphenols were significantly associated with a higher rectal cancer in women

217 (HR_{log2} = 1.25, 95 % CI 1.10 - 1.41) but not in men (HR_{log2} = 1.08, 95 % CI 0.95 -
218 1.23) (P_{sex-interaction} = 0.026).

219 For CRC, no statistically significant relationships were observed between any of
220 the classes and subclasses of polyphenols neither in women nor in men (**Table**
221 **3**). For colon cancers, inverse associations with the intake of total phenolic
222 acids (HR_{log2} = 0.91, 95 % CI 0.85 - 0.97; P=0.005) (P_{sex-interaction} < 0.001) and its
223 main subclass hydroxycinnamic acids (HR_{log2} = 0.92, 95 % CI 0.87 - 0.97;
224 P=0.004), as well as for methoxyphenols (HR_{log2} = 0.99, 95 % CI 0.98 – 1.00;
225 P=0.007) were found only in men. For rectal cancers, positive associations
226 were observed in women with the intake of phenolic acids (HR_{log2} = 1.10, 95 %
227 CI 1.02 - 1.19; P=0.013) (P_{sex-interaction} = 0.22), and its subclasses
228 hydroxybenzoic acids (HR_{log2} = 1.05, 95 % CI 1.00 - 1.10; P=0.039), and
229 hydroxycinnamic acids (HR_{log2} = 1.07, 95 % CI 1.00 - 1.15; P=0.038), as well as
230 for flavanones (HR_{log2} = 1.03, 95 % CI 1.00 - 1.07; P=0.048),
231 alkylmethoxyphenols (HR_{log2} = 1.04, 95 % CI 1.00 - 1.08; P=0.031), and
232 methoxyphenols (HR_{log2} = 1.02, 95 % CI 1.00 - 1.03; P=0.036). In women, a
233 significant positive association was also detected between the risk of rectal
234 cancer and flavonoid intake using the continuous variable (HR_{log2} = 1.09, 95 %
235 CI 1.00 - 1.18; P=0.039), but not using the quintiles (HR_{Q5 vs Q1} = 1.23, 95 % CI
236 0.94 - 1.60; P-trend=0.41). In men, an inverse association was found between
237 hydroxybenzaldehyde intake and rectal cancer (HR_{log2} = 0.97, 95 % CI 0.95 –
238 1.00; P=0.035). However, none of these associations exceeded the Bonferroni
239 significance threshold.

240 There were no evidence that age, BMI, and baseline alcohol intake modified the
241 association between total polyphenol intake and CRC risk in the multivariable

242 models. Since a statistically significant interaction between smoking status
243 (never, former, and current smoker) and total polyphenol ($P_{\text{interaction}} = 0.033$) and
244 flavonoid ($P_{\text{interaction}} = 0.037$) intake in relation to CRC risk was observed in
245 women, we stratified the statistical models by smoking status (**Supplementary**
246 **table 2**). In most of cases, stronger associations were detected in either never
247 or current smokers, although the results obtained were similar to those of the
248 entire cohort.

249 In additional analysis, the relationships between the intake of total polyphenols
250 and their main classes (flavonoids and phenolic acids) and the risk of overall
251 CRC and by anatomical subsite (colon and rectal cancers) (**Figure 1**) were
252 performed by length of follow-up [at 3 years, 6 years, 9 years, 12 years, 15
253 years, 18 years, and maximum of follow-up (22.8 years)]. When censoring data
254 at 3 years of follow-up, no associations were observed. At 6 years, all
255 associations were similar to those found after the longest follow-up, although
256 not all of them were statistically significant. The strongest results were found
257 censoring data at 9 years of follow-up, while in longer follow-ups (>9 years) the
258 associations were progressively attenuated.

259 In a separate sensitivity analysis in which the 462 CRC cases diagnosed within
260 the first 2 years of follow-up were excluded, the associations between the intake
261 of total polyphenols and polyphenol classes and overall CRC risk and by
262 anatomical subsite were practically identical to results based on the whole
263 cohort (data not shown).

264 **DISCUSSION**

265 In the present European prospective multi-country study, no statistically
266 significant association between total polyphenol intake and overall CRC risk
267 was observed. This is in line with findings of the Fukuoka colorectal case-
268 control study (15). However, we observed a suggestive inverse association
269 between total polyphenols intake and colon cancer risk in men and a positive
270 one with rectal cancer risk in women. These findings for total polyphenol intake
271 were almost identical to those found for phenolic acid intake.

272 Phenolic acids are the main contributors to total polyphenol intake (49.0% and
273 54.7% in Mediterranean and non-Mediterranean EPIC countries, respectively)
274 and coffee is, by far, their principal food source (70.6-74.6%) (17). In the current
275 study, we did not see an association between phenolic acid intake and CRC risk
276 in either men or women. Similar results were also observed after adjustment for
277 coffee intake, implying that other food sources of phenolic acids were not
278 related to CRC risk. In a nested case-control study within EPIC, no associations
279 were found between concentrations of phenolic acids in plasma (including
280 caffeic and ferulic acids which are major phenolic acids associated with coffee
281 intake) (25) and colon cancer risk, except that homovanillic acid was associated
282 with an increased risk (26). Plasma homovanillic acid is most probably
283 associated with the metabolism of catecholamines and cannot be directly linked
284 to phenolic acid intake. In the Fukuoka colorectal case-control study a
285 borderline statistically significant inverse association between coffee polyphenol
286 intake (which accounts for most phenolic acids) and colon cancer risk was
287 reported in both sexes, but not for rectal cancer risk (15). In the EPIC study, null
288 results were previously shown between coffee intake and overall CRC risk (27)
289 and CRC mortality (28), although inverse associations with colon cancer risk in

290 men and positive associations with rectal cancer risk in women (27) and CRC
291 mortality in women (28) were noted. In two recent meta-analyses, coffee intake
292 was not associated with the risk of both overall CRC and rectum cancers in
293 cohort studies (29;30); although higher doses of coffee (>5cups/day) has been
294 reported to decrease the risk of colon cancer (30). However, the evidence is
295 inconsistent; in an Australian-based case-control study, iced coffee
296 consumption was associated with a higher risk of rectal cancer (31).
297 Interestingly, in a recent meta-analysis of coffee intake, including 8 Japanese
298 cohorts, a significant decreased risk of colon cancer was observed in women,
299 but not in men (32). Moreover, no association was observed with rectal cancer
300 risk in both sexes; although a significant increase was detected after excluding
301 cases diagnosed within 3 years of the baseline only in women. Despite the
302 suggestive epidemiological evidence regarding sex and anatomical location,
303 there is heterogeneity in the association between phenolic acid and coffee in
304 relation to CRC, thus further research is needed to confirm these results and to
305 elucidate the underlying mechanisms of action. Part of these discrepancies
306 might be because different types of coffee have different polyphenol
307 compositions and contents, which are difficult to take into account in large
308 epidemiological studies, such as in EPIC (33). In an Israeli-based case-control
309 study, a significant inverse association was found between CRC risk and the
310 intake of boiled and espresso coffees but not instant and filter coffees, with
311 stronger associations for colon cancer (34). Phenolic acid intake is highly
312 correlated with coffee intake (35) and therefore, other coffee constituents such
313 as caffeine, cafestol and kahweol may also contribute to any association with
314 CRC risk (36). No associations between total, caffeinated or decaffeinated

315 coffee and CRC risk were found in the Prostate, Lung, Colorectal, and Ovarian
316 Cancer Screening Trial (37). Indeed, CYP1A2 and NAT2 genotypes, enzymes
317 involved in caffeine metabolism, did not affect associations between coffee
318 consumption and CRC risk (27). Therefore, caffeine does not seem to play a
319 role in CRC pathogenesis. Another potential explanation for these differences in
320 the relationships between cancer sites and sexes is due to endogenous factors,
321 such as metabolic heterogeneity and gut microbiota, which may influences
322 coffee bioavailability and therefore the bioactivity and bioefficacy of its
323 constituents. Gut microbiota composition slightly varies between sexes (38),
324 and especially, depend on the interaction between sex and diet (39).

325 We did not observe clear associations between flavonoid intake, the second
326 major contributor to total polyphenols (44.3%), and CRC risk, and anatomical
327 subsites in both men and women. These results were in concordance with our
328 previous study with shorter follow-up (13), and three meta-analyses of
329 prospective studies (40-42), although some protective associations have been
330 systematically reported in case-control studies (41;42). In these prospective
331 studies and in agreement with the present findings, no association was
332 observed either with any of the flavonoid subclasses. However, some inverse
333 associations have been reported between CRC risk and specific flavonoid
334 compounds such as tea polyphenols and isoflavones. Urinary biomarkers of
335 green tea polyphenols were also associated with a reduced risk of developing
336 colon cancer in Chinese men (43); however, in Europe black tea is the type
337 usually consumed. Plasma equol concentration, but not other isoflavones, was
338 inversely related to colon cancer risk in a previous nested case-control study
339 within EPIC (26). In contrast, no association was found with plasma and urinary

340 isoflavone levels in the EPIC-Norfolk study (44) or with dietary isoflavone
341 intakes in a meta-analysis of cohort studies (11).

342 No association between lignan intake and CRC risk was observed in our study,
343 as previously reported in a meta-analysis of cohort studies. No association was
344 found with urinary and plasma lignan concentrations in EPIC (26;44) and in a
345 Dutch cohort (45). However an inverse association between intakes of dietary
346 enterolignan and enterodiol and CRC risk were found in women but not in men
347 from EPIC-Norfolk (44).

348 No significant association between any minor subclasses of polyphenols and
349 CRC risk was observed in our study. Methoxyphenols (guaiacol is the only
350 polyphenol in this class) showed a similar pattern of associations to phenolic
351 acids, because the main food source is coffee (17). In agreement with present
352 observations, plasma concentrations of stilbenes and tyrosols were not related
353 to colon cancer (26), although an inverse association between plasma
354 alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and distal
355 colon cancer risk (46) was observed in a previous nested case-control study
356 within EPIC.

357 We also investigated the relationships between polyphenol intake and CRC risk
358 over the years of follow-up. The strongest associations were found from 6 to 9
359 years of follow-up, which may be the presumable period of progression from
360 asymptomatic precancerous polyps to CRC (47;48). Results from longer follow-
361 ups tended to be attenuated, which could be due to misclassification bias. The
362 longer the follow-up the higher the chance of change of dietary and lifestyle
363 habits by the participants. This can be evaluated with periodic reassessments of

364 the main exposure and the cofounders. Despite this attenuation, our findings
365 after a mean of 14 years of follow-up maintained their significance because
366 accrual of more cases meant there was greater statistical power to detect
367 associations.

368 The major strengths of the present study are its prospective design, its long
369 follow-up, its large size and number of cases, and the coverage of several
370 European countries with large dietary heterogeneity. This study also has
371 several potential limitations. First, diet and other lifestyle variables were only
372 available at baseline, and therefore, changes in these variables could not be
373 taken into account in these analyses. The second limitation may be the
374 measurement error in collecting dietary intake, but centre/country-specific
375 validated questionnaires for polyphenol-rich foods were used (19). Moreover,
376 the Phenol-Explorer is the most comprehensive food composition database on
377 polyphenols available nowadays (16). The third limitation is the potential
378 modification of diet during the early prediagnostic period of the disease;
379 however, sensitivity analyses excluding incident cases diagnosed in the first 2
380 years of follow-up did not alter the associations. The fourth limitation is the
381 potential impact of residual confounding, since several lifestyle and other dietary
382 factors related to CRC were different according to polyphenol intake. Although
383 we have included them in the statistical models, measurement error and
384 changes during follow-up may affect our results. Finally, we realize that our
385 study is prone to the well-known drawback of multiple comparisons. We have
386 therefore applied the Bonferroni correction and none of the tested associations
387 remained statistically significant. Despite this rather conservative method, we
388 were still able to observe borderline statistically significant associations.

389 In summary, we found that higher intakes of phenolic acids, reflecting high
390 coffee consumption, were associated with a lower risk of colon cancer in men
391 and a higher risk of rectal cancer in women, although the findings were no
392 longer significant after Bonferroni correction. Further studies are warranted to
393 evaluate the potential role of the intakes of phenolic acids and coffee in CRC
394 development.

395

396 **CONFLICT OF INTEREST**

397 The authors declare that they have no conflict of interest.

398 **ACKNOWLEDGEMENTS**

399 We thank Mr Bertrand Hémon for his valuable help with the EPIC database. We
400 also acknowledge the Northern Sweden Diet Database.

401 **FUNDING**

402 This study was supported by the Institut National du Cancer, Paris (INCa grants
403 2011-105). The coordination of EPIC is financially supported by the European
404 Commission (DG-SANCO) and the International Agency for Research on
405 Cancer. The national cohorts are supported by Danish Cancer Society
406 (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale
407 de l'Education Nationale, Institut National de la Santé et de la Recherche
408 Médicale (INSERM) (France); German Cancer Aid, German Cancer Research
409 Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche
410 Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of
411 Education and Research (Germany); the Hellenic Health Foundation (Greece);
412 Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National
413 Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports
414 (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch
415 Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer
416 Research Fund (WCRF), Statistics Netherlands (The Netherlands); European
417 Research Council (ERC-2009-AdG 232997); Health Research Fund (FIS):
418 PI13/00061 to Granada; PI13/01162 to EPIC-Murcia, Regional Governments of

419 Andalucía, Asturias, Basque Country, Murcia and Navarra, AGAUR -
420 Generalitat de Catalunya (exp. 2014 SGR 726), The Health Research Funds
421 RD12/0036/0018, cofunded by European Regional Development Fund (ERDF)
422 “A way to build Europe (Spain); the Swedish Research Council for Health,
423 Working Life and Welfare (FORTE), Swedish Cancer Society, Swedish
424 Research Council (VR) and County Councils of Skåne and Västerbotten
425 (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and
426 C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-
427 Norfolk, MR/M012190/1 to EPIC-Oxford) (United Kingdom). RZ-R was
428 supported by the “Miguel Servet” program (CP15/00100) from the Institute of
429 Health Carlos III and European Social Fund (ESF).

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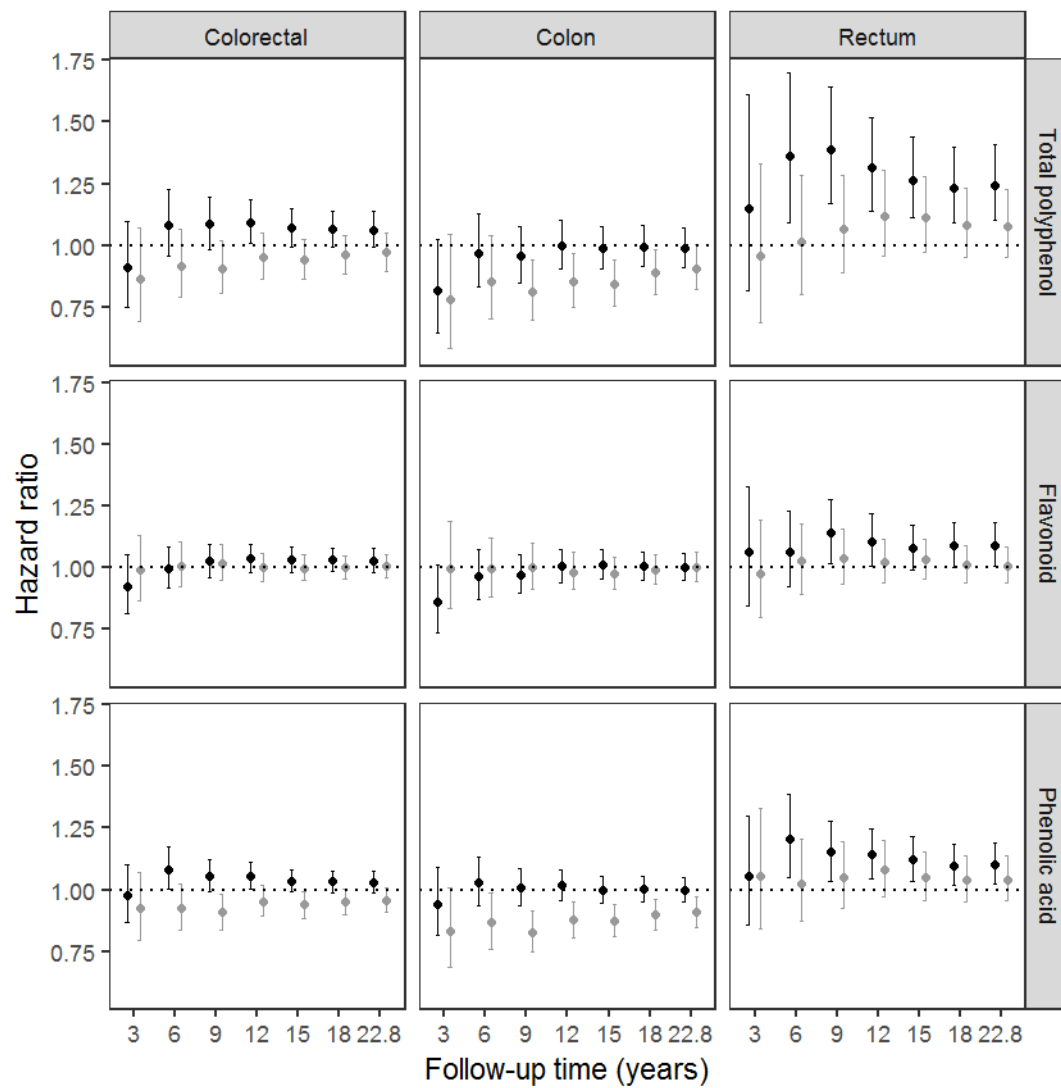


Figure 1. Hazard ratios and (95% CI) for colorectal cancer and subsites by sex and length of follow-up, according to double the intake (\log_2) of total polyphenol, flavonoid, and phenolic acid in women (black circles) and men (grey circles) from the EPIC study.

Table 1. Distribution of subjects and colorectal cancer cases according to anatomical subsite and medians (5th–95th percentiles) of total polyphenol intake in 10 participating countries in the EPIC Study.

Country	N	Colorectal cancer cases, N						Polyphenol intake (mg/d)	Flavonoid intake (mg/d)	Phenolic acid intake (mg/d)
		Overall	Colon	Proximal	Distal	NOS	Rectum			
Women										
Denmark	28,720	533	363	170	161	32	170	1,552 (802-2,481)	514 (133-1,459)	890 (320-1,547)
France	67,403	410	264	129	125	10	146	1,320 (552-2,603)	514 (188-1,226)	679 (165-1,848)
Germany	27,379	177	121	66	53	2	56	1,033 (549-1,927)	414 (153-1,051)	504 (194-1,074)
Greece	15,233	41	25	11	7	7	16	759 (345-1,556)	247 (101-528)	416 (105-1,105)
Italy	30,513	342	264	119	116	29	78	853 (443-1,438)	413 (175-791)	377 (118-757)
Norway	33,975	297	195	104	86	5	102	653 (263-1,090)	184 (61-400)	371 (66-844)
Spain	24,850	218	154	57	79	18	64	671 (254-1,407)	282 (80-684)	311 (61-907)
Sweden	26,368	442	305	182	108	15	137	838 (418-1,465)	272 (89-678)	488 (166-971)
The Netherlands	26,912	387	268	154	109	5	119	1,158 (631-1,760)	514 (185-1,008)	574 (186-985)
United Kingdom	52,566	555	381	216	132	33	174	1,443 (662-2,240)	873 (317-1,495)	469 (129-1,054)
TOTAL	333,919	3,402	2,340	1,208	976	156	1,062	1,054 (415-2,148)	420 (116-1,239)	508 (123-1,318)
Men										
Denmark	26,294	709	395	161	202	32	314	1,594 (809-2,460)	397 (107-1,271)	993 (359-1,629)
France	-	-	-	-	-	-	-	-	-	-
Germany	21,178	258	141	59	67	15	117	1,093 (554-2,079)	402 (140-1,056)	549 (199-1,226)
Greece	10,815	51	31	10	10	11	20	967 (469-1,921)	302 (126-614)	538 (153-1,377)
Italy	14,032	228	160	55	86	19	68	1,009 (522-1,695)	493 (202-964)	428 (156-805)
Norway	-	-	-	-	-	-	-	-	-	-
Spain	15,139	339	220	81	126	13	119	834 (333-1,725)	425 (118-1,085)	315 (92-769)
Sweden	22,306	473	284	142	136	6	189	888 (442-1,568)	252 (75-664)	544 (193-1,064)

The Netherlands	9,627	119	58	29	26	3	61	1,155 (601-1,854)	398 (137-910)	674 (178-1,198)
United Kingdom	22,850	412	268	132	114	22	144	1,509 (735-2,309)	916 (334-1,519)	517 (157-1,076)
TOTAL	142,241	2,589	1,557	669	767	121	1,032	1,150 (505-2,159)	419 (117-1,246)	562 (162-1,396)

Table 2. HRs (95% CIs) for colorectal cancer (CRC) and subsites, according to quintile of intake of total polyphenols in women and men from the EPIC study.

		Overall CRC HR (95% CI)	Colon HR (95% CI)	Proximal HR (95% CI)	Distal HR (95% CI)	P- value ¹	Rectum HR (95% CI)	P- value ²
Women								
Model 1	Quintile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)		1.00 (ref)	
	Quintile 2	1.00 (0.89-1.13)	0.96 (0.83-1.10)	1.02 (0.84-1.24)	0.86 (0.70-1.06)		1.13 (0.91-1.40)	
	Quintile 3	1.11 (0.99-1.26)	1.02 (0.89-1.18)	1.06 (0.87-1.30)	0.96 (0.77-1.19)		1.37 (1.10-1.71)	
	Quintile 4	1.10 (0.97-1.25)	0.99 (0.85-1.16)	1.14 (0.92-1.41)	0.81 (0.64-1.02)		1.39 (1.10-1.76)	
	Quintile 5	1.12 (0.98-1.28)	0.99 (0.85-1.17)	1.12 (0.89-1.41)	0.85 (0.66-1.09)		1.45 (1.34-1.86)	
	P-trend	0.09	0.93	0.26	0.22		0.004	
	Continuous (log ₂)	1.06 (0.99-1.13)	0.99 (0.92-1.07)	1.05 (0.94-1.16)	0.92 (0.83-1.03)	0.11	1.22 (1.09-1.37)	0.002
Model 3	Quintile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)		1.00 (ref)	
	Quintile 2	1.00 (0.89-1.13)	0.96 (0.83-1.10)	1.02 (0.84-1.24)	0.86 (0.70-1.07)		1.13 (0.91-1.41)	
	Quintile 3	1.12 (0.99-1.26)	1.02 (0.88-1.18)	1.05 (0.86-1.30)	0.97 (0.78-1.21)		1.39 (1.11-1.74)	
	Quintile 4	1.10 (0.97-1.26)	0.99 (0.85-1.17)	1.13 (0.90-1.41)	0.82 (0.64-1.06)		1.41 (1.10-1.80)	
	Quintile 5	1.13 (0.97-1.30)	1.00 (0.83-1.19)	1.11 (0.86-1.42)	0.87 (0.66-1.14)		1.49 (1.14-1.94)	
	P-trend	0.10	0.92	0.35	0.36		0.006	
	Continuous (log ₂)	1.06 (0.99-1.14)	0.99 (0.91-1.07)	1.04 (0.93-1.17)	0.93 (0.82-1.06)	0.22	1.25 (1.10-1.41)	0.002
Men								
Model 1	Quintile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)		1.00 (ref)	
	Quintile 2	1.02 (0.90-1.16)	1.08 (0.92-1.27)	0.95 (0.74-1.22)	1.23 (0.98-1.54)		0.92 (0.75-1.13)	
	Quintile 3	0.96 (0.84-1.10)	1.02 (0.86-1.21)	0.94 (0.73-1.20)	1.14 (0.90-1.44)		0.88 (0.71-1.08)	
	Quintile 4	0.94 (0.82-1.08)	0.93 (0.78-1.11)	0.81 (0.62-1.06)	1.07 (0.83-1.37)		0.95 (0.77-1.18)	
	Quintile 5	0.89 (0.77-1.02)	0.82 (0.68-0.99)	0.78 (0.59-1.03)	0.84 (0.64-1.11)		0.97 (0.78-1.22)	
	P-trend	0.05	0.010	0.05	0.07		0.94	
	Continuous (log ₂)	0.94 (0.88-1.01)	0.88 (0.81-0.97)	0.85 (0.74-0.97)	0.91 (0.80-1.04)	0.43	1.05 (0.93-1.17)	0.022

Model 3	Quintile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
	Quintile 2	1.03 (0.91-1.17)	1.10 (0.93-1.29)	0.95 (0.74-1.22)	1.27 (1.01-1.59)	0.93 (0.75-1.14)	
	Quintile 3	0.97 (0.85-1.11)	1.04 (0.87-1.23)	0.93 (0.72-1.21)	1.18 (0.92-1.51)	0.88 (0.71-1.10)	
	Quintile 4	0.96 (0.83-1.11)	0.95 (0.79-1.15)	0.80 (0.61-1.06)	1.12 (0.86-1.46)	0.96 (0.77-1.21)	
	Quintile 5	0.94 (0.80-1.10)	0.89 (0.72-1.09)	0.79 (0.58-1.08)	0.95 (0.71-1.28)	1.01 (0.79-1.29)	
	P-trend	0.30	0.09	0.10	0.36	0.65	
	Continuous (log ₂)	0.97 (0.90-1.05)	0.91 (0.82-1.01)	0.85 (0.73-0.99)	0.97 (0.84-1.12)	0.21	1.08 (0.95-1.23) 0.036

¹P-value for heterogeneity for proximal vs distal colon cancer

²P-value for heterogeneity for colon vs rectum cancer

Model 1: Cox model was stratified by age and centre.

Model 3: Cox model was additionally adjusted for smoking status and intensity, physical activity, education level, body mass index, total energy intake, alcohol, red and processed meat, fibre (g/d) and calcium (mg/d) intakes and in women also for menopausal status, hormone replacement therapy use, and oral contraceptive use.

Table 3. Hazard ratios (95% CIs) for colorectal cancer and subsites, according to double the intake of polyphenol classes and subclasses by sex in the EPIC study.

	Women					Men					
	Intake (mg/d) median (P5%-P95%)	Colorectal HR (95% CI)	Colon HR (95% CI)	Rectum HR (95% CI)	P-value ¹	Intake (mg/d) median (P5%-P95%)	Colorectal HR (95% CI)	Colon HR (95% CI)	Rectum HR (95% CI)	P-value ¹	P-value ²
Flavonoid subclasses	419.7 (116.3-1238.9)	1.03 (0.98-1.08)	1.00 (0.95-1.06)	1.09 (1.00-1.18)*	0.10	418.8 (117.4-1245.8)	1.00 (0.96-1.05)	1.00 (0.94-1.06)	1.01 (0.94-1.09)	0.87	0.030
Anthocyanins	25.5 (3.7-116.1)	1.01 (0.99-1.04)	1.00 (0.97-1.03)	1.02 (0.97-1.06)	0.46	22.9 (2.8-120.5)	0.99 (0.97-1.01)	1.00 (0.97-1.02)	0.98 (0.95-1.01)	0.49	0.09
Dihydrochalcones	1.8 (0.1-6.3)	1.00 (0.99-1.02)	1.00 (0.99-1.02)	1.01 (0.98-1.03)	0.76	1.5 (0.1-6.9)	1.00 (0.99-1.01)	0.99 (0.98-1.01)	1.00 (0.98-1.01)	0.61	0.038
Dihydroflavonols	0.4 (0.0-9.6)	1.00 (1.00-1.01)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	0.20	1.0 (0.0-18.4)	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.98-1.00)	0.64	0.027
Flavanols	285.6 (62.4-1015.5)	1.02 (0.98-1.06)	1.00 (0.95-1.04)	1.05 (0.98-1.13)	0.19	283.5 (65.1-1028.8)	1.01 (0.97-1.05)	0.99 (0.94-1.04)	1.01 (0.95-1.08)	0.51	0.043
Flavan-3-ol monomers	39.8 (6.4-460.4)	1.01 (0.99-1.03)	0.99 (0.97-1.02)	1.04 (1.00-1.09)	0.08	42.8 (7.4-466.1)	1.00 (0.97-1.02)	0.99 (0.96-1.02)	1.00 (0.96-1.04)	0.63	0.08
Proanthocyanidins	202.9 (52.4-532.0)	1.04 (0.99-1.08)	1.01 (0.96-1.07)	1.06 (0.98-1.15)	0.29	203.7 (51.5-552.1)	1.00 (0.96-1.05)	0.99 (0.93-1.04)	1.00 (0.93-1.07)	0.56	0.020
Theaflavins	1.6 (0.0-106.4)	1.00 (1.00-1.01)	1.00 (1.00-1.00)	1.01 (1.00-1.01)	0.26	1.5 (0.0-112.0)	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (1.00-1.01)	0.74	0.06
Flavanones	25.6 (1.8-118.3)	1.00 (0.99-1.02)	0.99 (0.97-1.02)	1.03 (1.00-1.07)*	0.05	24.2 (2.2-120.0)	0.99 (0.97-1.01)	0.99 (0.96-1.01)	1.00 (0.96-1.03)	0.69	0.10
Flavones	9.3 (2.7-26.6)	1.02 (0.98-1.06)	1.02 (0.97-1.07)	1.02 (0.95-1.10)	0.09	9.4 (2.3-30.4)	0.98 (0.94-1.03)	0.96 (0.91-1.02)	0.97 (0.90-1.04)	0.42	0.027
Flavonols	27.9 (6.9-112.0)	1.01 (0.97-1.05)	0.99 (0.94-1.04)	1.07 (0.99-1.15)	0.08	29.5 (7.9-113.3)	1.01 (0.96-1.05)	0.99 (0.94-1.05)	1.00 (0.93-1.07)	0.57	0.23
Isoflavonoids	0.0 (0.0-7.3)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.00 (0.99-1.02)	0.48	0.0 (0.0-5.0)	0.99 (0.98-1.01)	0.99 (0.98-1.00)	1.00 (0.98-1.02)	0.28	0.001
Phenolic acid subclasses	508.2 (122.8-1317.8)	1.03 (0.99-1.08)	1.00 (0.95-1.05)	1.10 (1.02-1.19)*	0.038	561.9 (162.1-1395.7)	0.96 (0.91-1.01)	0.91 (0.85-0.97)**	1.04 (0.95-1.14)	0.015	0.001
Hydroxybenzoics	19.5 (1.3-155.0)	1.00 (0.98-1.03)	0.99 (0.96-1.02)	1.05 (1.00-1.10)*	0.03	23.0 (3.1-159.5)	1.00 (0.97-1.04)	1.00 (0.96-1.04)	1.01 (0.96-1.06)	0.93	0.10
Hydroxycinnamic	474.6 (95.5-1279.3)	1.02 (0.98-1.06)	1.01 (0.96-1.05)	1.07 (1.00-1.15)*	0.10	513.6 (118.2-1356.5)	0.96 (0.92-1.01)	0.92 (0.87-0.97)**	1.03 (0.96-1.11)	0.017	0.002
Hydroxyphenylacetic	0.1 (0.0-0.6)	0.99 (0.98-1.01)	0.99 (0.98-1.01)	1.00 (0.98-1.03)	0.54	0.2 (0.0-1.3)	1.00 (0.98-1.01)	0.99 (0.97-1.01)	0.98 (0.96-1.01)	0.12	0.40
Stilbenes	0.4 (0.0-6.6)	1.00 (0.98-1.01)	1.00 (0.98-1.02)	1.00 (0.97-1.03)	0.74	0.8 (0.0-11.8)	0.98 (0.96-0.99)	0.98 (0.96-1.00)	0.97 (0.95-1.00)	0.70	0.042
Lignans	1.4 (0.7-4.9)	1.01 (0.94-1.08)	0.98 (0.90-1.06)	1.08 (0.95-1.21)	0.20	1.6 (0.8-5.3)	1.06 (0.98-1.15)	1.11 (1.01-1.22)	0.99 (0.86-1.13)	0.17	0.83
Other polyphenol classes											
Alkylphenols	24.4 (2.0-80.1)	1.00 (0.97-1.03)	1.00 (0.97-1.04)	1.00 (0.95-1.06)	0.95	39.7 (2.3-113.5)	0.99 (0.96-1.02)	0.99 (0.95-1.02)	1.01 (0.95-1.06)	0.57	<0.001
Tyrosol	3.5 (0.3-30.2)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	0.97 (0.94-1.00)	0.26	4.5 (0.4-49.8)	0.99 (0.97-1.01)	1.00 (0.97-1.02)	0.97 (0.94-1.00)	0.22	0.20
Alkylmethoxyphenols	2.2 (0.1-6.2)	1.01 (0.99-1.02)	1.00 (0.98-1.02)	1.04 (1.00-1.08)*	0.036	2.7 (0.3-7.3)	0.99 (0.98-1.01)	0.99 (0.97-1.01)	1.00 (0.97-1.03)	0.49	0.005
Furanocoumarins	0.0 (0.0-0.4)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	0.99 (0.98-1.00)	0.39	0.0 (0.0-0.3)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.01 (0.99-1.02)	0.31	0.87
Hydroxybenzaldehydes	0.1 (0.0-1.5)	0.99 (0.98-1.01)	0.99 (0.98-1.01)	1.01 (0.98-1.03)	0.39	0.3 (0.0-2.5)	0.99 (0.98-1.01)	0.98 (0.96-1.00)	0.97 (0.95-1.00)*	0.10	0.008
Hydroxycoumarins	0.0 (0.0-0.4)	0.99 (0.99-1.00)	1.00 (0.99-1.01)	0.99 (0.98-1.01)	0.42	0.2 (0.0-1.3)	1.00 (0.99-1.01)	0.99 (0.98-1.01)	0.99 (0.98-1.00)	0.13	0.003
Hydroxyphenylpropenes	0.0 (0.0-4.0)	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.99-1.01)	0.59	0.2 (0.0-5.8)	1.00 (1.00-1.01)	1.01 (1.00-1.01)	1.00 (0.99-1.01)	0.22	0.18
Methoxyphenols	0.3 (0.0-0.8)	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.02 (1.00-1.03)*	0.17	0.3 (0.0-0.8)	0.99 (0.98-1.00)	0.99 (0.98-1.00)**	0.99 (0.98-1.00)	0.73	<0.001

*P-value<0.05; **P-value<0.01; any association exceeds the Bonferroni threshold ($P < 0.05/26$) < 0.002

¹P-value for heterogeneity for colon vs rectum cancer

²P-value for interaction by sex in colorectal cancer

Cox model was stratified by age and centre, and additionally adjusted for smoking status and intensity, physical activity, education level, body mass index, total energy intake, alcohol, red and processed meat, fibre (g/d) and calcium (mg/d) intakes and in women also for menopausal status , hormone replacement therapy use, and oral contraceptive use