Dietary polyphenols in the aetiology of Crohn's disease and ulcerative colitis – A multicenter European Prospective Cohort study (EPIC)

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Abstract

Background Oxidative stress may be involved in the aetiology of inflammatory disease (IBD) and whether dietary polyphenols, which possess antioxidants properties, prevent its development is unknown.

Methods A total of 401,326 men and women age 20-80 years from 8 countries were recruited between 1991 and 1998, and at baseline completed validated food frequency questionnaires. Dietary polyphenol intake was measured using Phenol-Explorer, a database with information on the content of 502 polyphenols. Incident cases of Crohn's diseases (CD) and ulcerative colitis (UC) were identified during the follow-up period of up to December, 2010. A nested case-control study using conditional logistic regression estimated the odds ratios (ORs), and 95% confidence intervals (CI), for polyphenol intake (categories based on quartiles) and developing CD or UC.

Results In total 110 CD (73% women) and 244 UC (57% women) cases were identified and matched to 440 and 976 controls, respectively. Total polyphenol intake was not associated with CD (P trend=0.17) or UC (P trend=0.16). For flavones and CD, there were reduced odds for all quartiles, which was statistically significant for the third ($OR_{3th\ vs\ 1st\ quartile}$ =0.33, 95% CI: 0.15, 0.69) and there was an inverse trend across quartiles (P=0.03). Similarly, for resveratrol, there was an inverse association with CD ($OR_{4th\ vs\ 1st\ quartile}$ =0.40, 95% CI: 0.20, 0.82) with an inverse trend across quartiles (P=0.02). No significant associations between subtypes of polyphenols and UC were found. Effect modification by smoking in CD was documented with borderline statistical significance.

Conclusion The data supports a potential role of flavones and resveratrol in CD; future aetiological studies should investigate these dietary components and further examine the potential for residual confounding.

Key words Polyphenols, Crohn's diseases, ulcerative colitis, anti-oxidants.

Introduction

The incidence of inflammatory bowel disease (IBD) namely ulcerative colitis (UC) and Crohn's disease (CD) is rising, particularly in westernized nations (1). IBD is an important clinical problem, as patients have to take medications life-long, may require surgery and can develop serious complications, such as colorectal cancer (2,3). The aetiology of IBD has yet to be elucidated, although probably involves an abnormal immunological response to gastrointestinal luminal antigens in a genetically susceptible host (2). Documented risk factors include a positive family history (3), smoking (4, 5) and dietary components including intake of n-3 and n-6 fatty acids (6-8).

There are plausible biological mechanisms for how dietary polyphenols may prevent several gastrointestinal diseases, including IBD (9). These bioactive compounds form a large group of related organic molecules in plants, and are most abundant in: fruits, some vegetables, tea, coffee, cocoa, wine, herbs and spices (10-12). Plant polyphenols are sub-classified according to the number of phenol rings in their chemical structure. The largest class is flavonoids which is further sub-divided into flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols. Other major polyphenol classes are the stilbenes (resveratrol), phenolic acids (including hydroxybenzoic acids and hydroxycinnamic acids), and lignans. The subclasses of polyphenols vary in different foods e.g. flavonols are widely present in berries, apples and red onions; flavanols are mainly found in tea, cocoa and chocolate; isoflavones are commonly available in soybeans; lignans are abundant in flaxseed and sesame seed; resveratrol is affluent in grapes and wine; flavones are contained mainly in thyme, rosemary and oregano.

A potential mechanism for how polyphenols may prevent IBD is through inhibiting the biological process of oxidative stress, and the associated damage to DNA, lipids and proteins.

The gastrointestinal mucosa is constantly exposed to luminal pro-oxidants in foods such as alcohol, cholesterol oxides and fatty acids. Polyphenol compounds ameliorate oxidative stress by acting as free radical scavengers and inducing cellular antioxidant defence modulating proteins and genes expression (13, 14). Furthermore, experimental evidence suggests that polyphenols may attenuate intestinal inflammation by reducing the expression of pro-inflammatory proteins through influencing mitogen-activated protein kinases (MAPKs) and the transcription factor nuclear factor kB (NF-kB) signalling pathways (15).

The molecular mechanisms for how polyphenols may prevent IBD need to be supported by population-based epidemiological studies, demonstrating that initially well people who eat lower amounts of polyphenols are more susceptible to developing UC and CD than those eating more of these micronutrients. To date, no such epidemiological investigations have investigated the polyphenol hypothesis, including prospective studies, the most robust observational study design in nutritional epidemiology. The aim of this aetiological investigation was to conduct the first such prospective cohort study investigating if dietary polyphenols are inversely associated with the development of IBD in participants enrolled into the European Prospective Investigation into Cancer and Nutrition Study (EPIC). Demonstrating associations would support encouraging higher dietary intakes of polyphenols to reduce the incidence of IBD, and possibly their assessment in randomised controlled trials as treatments in patients to improve clinical outcomes.

Methods

Study population

The methodology of the main EPIC study has been previously described (16); in brief, 520,000 men and women were recruited in 23 collaborating centres in 10 European countries during the

years 1991-1998. EPIC was originally designed to investigate habitual diet and the aetiology of common cancers in the general population. The EPIC-IBD study is a sub cohort of 401,326 initially healthy men and women without CD or UC at recruitment (supplementary table 1). The age of participants at recruitment ranged between 20 to 80 years in the 12 centres from 8 European countries namely: Denmark, Germany, Greece, France, Italy, the Netherlands, Sweden and the United Kingdom. At recruitment lifestyle factors were measured including habitual diet using country-specific food frequency questionnaires (FFQs) that included information on: smoking, alcohol intake and physical activity. The FFQs listed approximately 200 different foods and up to nine frequency of intake categories. From these FFQs, dietary polyphenol intake was assessed using the Phenol-Explorer database, which contains data on the content of 502 polyphenol compounds in 452 plant-based foods (17). The effects of cooking and food processing on the polyphenol content of foods were accounted for by applying polyphenol-specific retention factors from Phenol-Explorer to the relevant foods (17). A retention factor describes the loss or gain of a micronutrient during food processing e.g. a value of 0.40 means that 40% of the compound has been retained during processing.

In addition to total polyphenol intake, the four main subclasses, namely flavonoids, lignans, stilbenes and phenolic acids, were computed from Phenol Explorer. Total polyphenol content was calculated as the sum of the contents of the individual compounds expressed in mg/100g food fresh weight. All animal foods that contain no or only traces of polyphenols were excluded from the database. Total daily energy intake was also derived from the FFQs.

Follow-up and ascertainment of IBD

After recruitment, the sub-cohort was subsequently monitored until at least May 2004, and in some centres until December 2010, to identify incident cases of both CD and UC. New cases

of IBD were detected by several methods depending on the centre, namely local and national IBD registries, self-reported follow-up questionnaires, pathology databases and hospital in-patient records. All the clinical notes of potential cases were reviewed by local physicians to confirm the diagnoses. Those participants who developed indeterminate or microscopic colitis, or who had prevalent IBD at recruitment (including IBD diagnosed less than 18 months after recruitment) were excluded. The latter helped to ensure the nutritional data were more likely to represent habitual diet before the development of symptoms and the subsequent diagnosis of IBD.

Statistical analysis

The analysis was a nested case-control design within a prospective cohort study. Four controls per case were randomly selected and matched by age at recruitment (± 6 months), gender, date of recruitment into the study (± 3 months) and study centre. The controls were alive on the date of diagnosis of the matched case to ensure a similar follow-up time. Absolute differences in polyphenol intake between cases and controls were compared with either a student's t-test or Wilcoxon-Mann-Whitney test according to the nature of the distributions. The intakes of polyphenols were divided into quartiles across the distribution of the cohort. Conditional logistic regression calculated the odds ratios (OR) and 95% confidence intervals (95% CI) for the dietary intake of *total* polyphenols and the subtypes: flavonoids, lignans, stilbenes, phenolic acid and the development of CD and UC separately. All of the models were analysed by adjusting for total energy intake (continuous variable), dietary fat and protein. The latter adjustment did not alter the observed associations and therefore we only kept total energy in the final model. The models were adjusted by educational level (none/primary school, technical/professional school, secondary school, longer education (including university)) and smoking (never, current or former). As cigarettes contain pro-oxidants, effect modification by

smoking status (never smokers versus ever smokers) was evaluated. All analyses were performed using SAS (The SAS Statistical Package. version 9.3, SAS institute, Gary, NC).

Results

Overall, 110 incident cases of CD (73% women; mean age at diagnosis = 55.4 years, standard deviation (SD) 11.1) and 244 incident cases of UC (57% women; mean age at diagnosis 57.5 years, SD=10.3) were identified (Table 1). Being an ever smoker was more frequent among CD and UC cases than among controls (Table 1). There were no significant statistical differences in the median intakes of either total or any of the sub-types of polyphenols between cases and controls (total polyphenols and CD = 1091.6 mg/day vs 1164.8 mg/day; for UC = 1226.1 mg/day vs 1203.0 mg/day, respectively (Table 1)).

In the multivariable analysis for total polyphenol intake and CD, and using the first quartile as the reference category, lower odds were found for all higher quartiles, which was statistically significant in the third ($OR_{3 \text{ vs } 1 \text{ quartile}}$=0.38, 95% CI: 0.18, 0.79), but with no trend across quartiles (P value for trend =0.17) (Table 2). In subgroups of polyphenols, for flavones lower odds were documented in all quartiles and was statistically significant in the third (OR=0.33, 95% CI: 0.15, 0.69), with an inverse trend across quartiles (P for trend=0.03). Similarly, for resveratrol all higher quartiles were associated with lower odds, which was statistically significant for the second quartile ($OR_{2 \text{ vs } 1 \text{ quartile}}$ =0.47, 95% CI: 0.25, 0.90) and highest quartile (OR =0.40, 95% CI: 0.20, 0.82), with an inverse trend across quartiles (P=0.02). For most other polyphenol subtypes, there were inverse, but not statistically significant, associations with higher quartiles, and no trends across categories. For isoflavones, the third quartile was positively associated with the odds of CD ($OR_{3 \text{ vs } 1 \text{ quartile}}$ =2.26, 95% CI: 1.13-4.53), but no trend across categories (P=0.11). For total polyphenol intake and UC, there were no statistically significant associations (Table 3). For subtypes of polyphenols, there were no

associations within quartiles, apart from a higher odds ratio in the third quartile of flavanols ($OR_{3 \text{ vs } 1 \text{ quartile}}$ =1.71, 95%CI: 1.09, 2.69) and no trends across quartiles.

Further stratified analyses were conducted by smoking status since this may hypothetically modify the effects of polyphenols. For non-smokers, there were no associations with either total or subtypes of polyphenols with CD or UC (supplementary tables 2 & 3); the exceptions were an inverse association with the second quartile of lignans and CD ($OR_{2 \text{ vs } 1 \text{ quartile}}$ =0.06, 95% CI=0.01-0.39), and borderline statistical significant trends for UC with flavonols (p=0.08) and isoflavones (p=0.07). In ever smokers (former plus current smokers), there were borderline significant trends across quartiles for flavanones (P= 0.07), flavones (P=0.07) and lignans (P=0.06) for CD (table 4). In ever smokers, total polyphenol intake was positively associated with UC (P trend=0.05), although only the third quartile was statistically significant ($OR_{3 \text{ vs1 quartile}}$ =2.00, 95% CI:1.04, 3.85) (table 5). There were positive associations between phenolic acids and UC ($OR_{3 \text{ vs } 1 \text{ quartile}}$ =2.11, 95% CI:1.06, 4.22; $OR_{4 \text{ vs } 1 \text{ quartile}}$ =2.14, 95% CI:1.03, 4.46; P trend=0.05) due to the contribution of hydroxycinnamic acid ($OR_{3 \text{ vs } 1 \text{ quartile}}$ =2.01, 95% CI:0.99, 4.07; $OR_{4 \text{ vs } 1 \text{ quartile}}$ =2.35, 95% CI:1.13, 4.91; P tend=0.04).

Discussion

We found no associations between *total* dietary polyphenol intake and the odds of developing either CD or UC. However, certain subtypes of polyphenols, namely flavones and resveratrol, were associated with lower odds of CD. There was some evidence of effect modification in ever smokers with suggestive inverse associations for CD with flavanones, flavones and lignans, but no associations in non-smokers for both UC and CD. The plausible biological mechanisms, magnitudes of these effect sizes, biological gradients, temporal data collection and adjustment for potential confounders suggest that these inverse associations could be protective ones. Mechanistically, certain polyphenols may prevent CD through inhibiting oxidative stress (13), which in the intestinal tract may contribute to the pathogenesis and progression of IBD (18, 19).

Recent data reported a positive correlation between reactive oxygen species (ROS), reactive nitrogen species (RNS) and gastrointestinal mucosal inflammation, which was associated with increased pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin-17A (IL-17A) and interleukin -23(IL-23) (20).

The suggestion of effect modification for certain polyphenols and CD in smokers, a process which induces oxidative stress, but not in non-smokers, provides evidence for the role of this metabolic process in the aetiology of CD. Oxidative stress develops via mechanisms including bacteriologic and immunologic pathways, which may support the varying associations of polyphenols with CD and UC; for example, antibiotic treatment for CD but not UC, and the distinct immune responses of CD (TH1 cytokine profile) and UC (TH2 profile) (the TH1 cytokine profile is involved in immune response to infection but not TH2 profile) support a possible role for the gut microbiota in CD (21). Furthermore, specific polyphenols, such as stilbenes (particularly resveratrol) may alter the composition of the gut microbial ecosystem, as supported by evidence in rats (22). Moreover, patients with active CD, compared to active UC, may have higher levels of oxidative stress characterised by higher superoxide dismutase (SOD) activity leading to H_2O_2 production increasing lipid peroxidation, and inhibiting mitochondrial function (23). CD patients have higher $ONOO^-$ (peroxynitrite) content, a by-product of iNOS (the inducible isoform of nitric oxide synthases (NOS)) that is highly expressed in activated macrophages and neutrophils of colonic mucosa (24). Finally, polyphenols possess not only antioxidant properties but also other bioactive functions including vasodilatory, antiviral, antibacterial, anti-inflammatory and anticarcinogenic effects, as well modulating signalling pathways influencing inflammation such as phospholipase A2, cyclooxygenase, lipoxygenase and the induction of NF-kB and MAPK signalling pathways (25). Most polyphenols were associated with a decreased odds of CD, although the trends were only statistically significant for flavones and resveratrol. This may suggest either firstly

different polyphenols have varying biological activities in preventing CD, or secondly there were insufficient cases to detect significant associations in other groups. Experimental work to elucidate any differential properties of specific polyphenols and how these may influence aetiology, plus further cohort follow-up to accrue more cases is required to clarify if there are associations. In UC, there was a positive association between hydroxycinnamic acid and UC among ever smokers, but not non-smokers, although we are not aware of any biological mechanisms to explain this, and we cannot discount the possibility that this is a false positive result. Hydroxycinnamic acid is mainly obtained from coffee, and the possibility of residual confounding exists, if there is another component of coffee which increases the risk of UC.

No previous epidemiological studies, as far as we are aware, have investigated polyphenols in the aetiology of either CD or UC. However, other foods that contain these micronutrients such as fibre-rich vegetables and fruits, have been studied (12, 26). A meta-analysis (of 2 cohort studies, and 5 case-control studies) reported that total dietary fibre was associated with a decreased risk of CD (pooled OR=0.44 ,95CI: 0.29-0.69), but not UC (pooled OR=0.80, 9%%CI: 0.64-1.00) (27). This inverse association for CD with fibre may be due to micronutrients in plant-based foods, such as polyphenols. Another meta-analysis of 14 case-control studies documented that consumption of vegetables was inversely associated with the risk of UC, but not CD. However, in a sub-group analysis for vegetables and CD there was a significantly inverse association for studies carried out in Europe, but not in Asia (27). The inverse association with vegetables in the European population is consistent with our findings because some polyphenols e.g. lignans, are abundant in western foods. The increased odds associated with some categories of isoflavones in CD might be linked to other conditions, such as lactose intolerance often undiagnosed in IBD sufferers who avoid dairy foods but have increased intakes of soybean foods that are rich in isoflavones (28-30). To help clarify if inverse

associations do exist with polyphenols, further observational studies, ideally prospective cohort investigations are required.

This observational study has several methodological strengths and limitations. The strengths include the prospective cohort design, which minimised both selection bias and recall bias for dietary polyphenol intake; and a full and detailed assessment of dietary polyphenol intake was derived from interpreting the FFQ using the polyphenol database specifically developed for EPIC (17). FFQs do have several limitations compared to 24-hour dietary recall or food diaries, in that a set list of certain foods' portion sizes and frequencies of intake are listed, therefore not allowing for any variations in individuals' specific intakes. Dietary assessments using weighed records of intake over a set time are not pragmatic in large scale epidemiological studies. The online resource, Phenol-Explore (http://phenol-explorer.eu/) is the first comprehensive database on polyphenol content of foods to be used in epidemiological studies. The latest version also includes detailed data on the effects of food processing and cooking. A further methodological strength was that all the case notes of potential IBD patients were reviewed by physicians to confirm the diagnoses to reduce measurement bias. Follow-up bias should be minimal as the number of cases identified was similar to that in a large incidence study conducted in many European countries (31). However, more cases in the analyses, particularly according to smoking status, would have allowed a better estimate of the precision of effect sizes. Further follow-up of the cohort is now being planned, including in centres not in the original EPIC-IBD study. Our findings may only be applicable to a middle-aged to elderly patient group with IBD, although the peak prevalence of both UC and CD is in younger people. However, the results are generalizable in that we studied both male and female participants from 8 countries with variation in their dietary habits, and the site of disease in the gastrointestinal tract was similar to that expected. Residual confounding may exist, namely there are other variables, possibly

dietary or other health-conscious behaviour, associated with polyphenols which are actually the true aetiological exposures. Polyphenols are present in several foods including fruits and vegetables, and it may be other micronutrients in these food groups that actually influence risk. The EPIC-IBD study is continuing to investigate other dietary hypotheses and polyphenols will be adjusted for any new dietary variables for which associations are detected. Furthermore, participants' diet may change over time, and as we only had one dietary measure, namely that at recruitment, this could introduce measurement error, making any smaller associations difficult to detect. However, such measurement error would introduce an under-estimate of effect sizes, rather than a spurious over-estimate. Measurement error may be reduced by controlling for total energy intake. Relatively small numbers of cases, particularly according to smoking status would mean small effect sizes may not be identified and further cohort follow-up is required to detect such differences. The higher proportions of smoking in UC was unexpected and maybe because there was just one measure of smoking, namely at recruitment which was several years before diagnosis. This may be relevant if recent cessation of smoking before the development of symptoms is important in aetiology. Finally, in this investigation multiple comparisons between polyphenols and the odds of IBD were undertaken, which could result in false positive results. Although, this is possible, it is less likely as there are plausible biological mechanisms for the inverse associations, including the suggestion of effect modification in the smoking group, and for several of these micronutrients there were biological gradients for the ORs across quartiles.

In conclusion, we have reported higher intakes of some polyphenols, namely flavones and resveratrol, are associated with a lower risk of CD, but no associations with polyphenol intake for UC. In CD, inverse associations were documented for some sub-groups of polyphenols in smokers, but not non-smokers, supporting a role for oxidative stress in the aetiology. Residual confounding for other dietary variables associated with polyphenols is a possibility. Further

large prospective cohort studies are warranted to measure polyphenol intake and determine if the associations are consistent. If so, increasing the dietary intake of these micronutrients may help reduce the risk of developing CD, and support their assessment as therapies in patients with established disease.

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Table

Table 1 Characteristics of participants in a nested case-control study within the EPIC-IBD study

Category	Crohn's disease		Ulcerative colitis	
	Cases (n=110)	Controls (n=440)	Cases (n=244)	Controls (n=976)
Gender (female %)	80(72.7)	320(72.3)	140(57.4)	565(57.9)
Age at recruitment, years (mean ± SD)	50.1(10.8)	50.1(10.7)	51.7(10.5)	51.7(10.5)
Age at diagnosis years (mean ± SD)	55.4(11.1)	-	57.5(10.3)	-
Interval between recruitment & diagnosis (mean ± SD)	5.5(2.9)	-	5.8(3.3)	-
Education(%)				
Primary school	22(20.0)	107(24.3)	68(27.8)	253(26.0)
Technical/professional school	33(30.0)	96(21.8)	62(25.4)	246(25.2)
Secondary school	30(27.3)	105(23.9)	52(21.3)	201(21.0)
Longer education(including university)	25(22.7)	125(28.4)	54(22.1)	245(25.1)
Missing	0(0.0)	7(1.6)	8(3.3)	31(3.2)
Smoking status (n, %)		*		*
Never smoked	41(37.3)	209(47.5)	65(26.6)	418(42.8)
Former smoker	28(25.5)	121(27.5)	91(37.3)	281(28.8)
Current smoker	38(34.6)	107(24.3)	82(33.6)	255(26.1)
Missing	3(2.7)	3(0.7)	6(2.5)	22(2.3)
Daily median intakes (mg/day)(inter quartile range)				

Total polyphenols		1091.6(848.8, 1517.4)	1164.8(888.8,1517. 4)	1226.1(911.3,1598. 5)	1203.0(872.1,1595. 3)
Flavonoids		474.6(276.6, 770.6)	462.8(293.4,707.8)	512.2(306.6,739.8)	475.5(311.4,762.6)
	Anthocyanidins	25.7(9.9, 53.7)	30.4(13.8, 55.5)	23.7(11.5, 49.7)	24.0(11.5,49.0)
	Flavanols	318.4(192.6, 627.6)	327.8 (192.7, 527.1)	379.3(218.1, 581.1)	338.2(203.7,585.1)
	Flavonols	28.2(15.2, 56.9)	29.9(18.0, 52.7)	30.6(17.0,59.5)	31.5(17.8, 59.1)
	Flavanones	21.8(9.0, 48.9)	24.8(11.3, 51.7)	23.9(10.0,50.4)	26.1(10.5, 59.3)
	Flavones	7.7(5.2, 14.4)	9.5 (6.0, 14.1)	9.5(5.3,14.5)	8.9(5.1,14.5)
	Isoflavones	0.04(0.01, 0.11)	0.03(0.01, 0.08)	0.03(0.01-0.08)	0.03(0.01,0.08)
	Lignans	1.4(1.0, 2.0)	1.4(1.1, 1.9)	1.4(1.1, 2.0)	1.4(1.0,2.0)
Stilbenes		0.3(0.1, 1.3)	0.5(0.1, 2.1)	0.5(0.1-2.1)	0.4(0.1,2.1)
	Resveratrol	0.1(0.0, 0.2)	0.1(0.0, 0.2)	0.1(0.0-0.3)	0.1(0.0,0.2)
Phenolic acids		560.9(428.4, 806.9)	573.4(396.1, 815.0)	592.4(388.1,868.8)	571.3(365.0,821.3)
	Hydroxybenzoic acid	23.7(8.7, 79.0)	26.1(11.1, 65.9)	27.9(8.4, 82.7)	28.6(10.4,79.8)
	Hydroxycinnamic acid	522.0(328.3. 777.4)	529.3(341.1, 770.5)	546.9(340.4,818.4)	518.4(301.0,777.3)
	Hydroxyphenylacetic	0.1(0.0, 0.3)	0.1(0.0, 0.3)	0.1(0.0,0.34)	0.1(0.0,0.3)

* $p<0.05$

Table 2. Odds ratios (OR) of developing Crohn's disease according to quartiles of polyphenol intakes

Polyphenols		Quartile of Intake				P value for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total polyphenols	Cases(n)	32	30	17	31	
	OR (95%CI)	1.00	0.78(0.41,1.47)	0.38(0.18,0.79)*	0.70(0.33,1.49)	0.17
Flavonoids	Cases(n)	32	23	23	32	
	OR (95%CI)	1.00	0.76(0.41,1.43)	0.72(0.37,1.38)	0.94(0.45,1.97)	0.71
Anthocyanidins	Cases(n)	36	26	20	28	
	OR (95%CI)	1.00	0.80(0.43,1.48)	0.56(0.29,1.11)	0.67(0.33,1.36)	0.18
Flavanols	Cases(n)	28	32	18	32	
	OR (95%CI)	1.00	1.14(0.63,2.05)	0.67(0.34,1.34)	1.11(0.51,2.42)	0.75
Flavonols	Cases(n)	31	26	22	31	
	OR (95%CI)	1.00	0.80(0.42,1.51)	0.68(0.32,1.44)	1.00(0.45,2.22)	0.89
Flavanones	Cases(n)	37	24	23	26	
	OR (95%CI)	1.00	0.64(0.35,1.17)	0.57(0.30,1.10)	0.60(0.32,1.13)	0.11
Flavones	Cases(n)	36	32	12	30	
	OR (95%CI)	1.00	0.88(0.49,1.60)	0.33(0.15,0.69)*	0.61(0.28,1.30)	0.03*
Isoflavones	Cases(n)	22	20	40	28	
	OR (95%CI)	1.00	0.98(0.50,1.92)	2.26(1.13,4.53)*	1.59(0.72,3.49)	0.11
Lignans	Cases(n)	36	18	27	29	
	OR (95%CI)	1.00	0.47(0.24,0.93)*	0.71(0.37,1.38)	0.67(0.30,1.48)	0.43
Stilbenes	Cases(n)	37	32	25	21	
	OR (95%CI)	1.00	0.91(0.50,1.66)	0.67(0.35,1.28)	0.53(0.26,1.08)	0.05
Resveratrol	Cases(n)	40	20	29	21	
	OR (95%CI)	1.00	0.47(0.25,0.90)*	0.60(0.32,1.11)	0.40(0.20,0.82)*	0.02*
Phenolic acids	Cases(n)	24	32	28	26	

	OR (95%CI)	1.00	1.21(0.65,2.27)	1.11(0.58,2.11)	0.83(0.41,1.69)	0.55
Hydroxybenzoic acid	Cases(n)	30	27	24	29	
	OR (95%CI)	1.00	0.82(0.43,1.59)	0.77(0.37,1.59)	0.85(0.37,1.95)	0.66
Hydroxycinnamic acid	Cases(n)	25	32	26	27	
	OR (95%CI)	1.00	1.23(0.67,2.28)	0.95(0.50,1.82)	0.91(0.46,1.79)	0.60
Hydroxyphenylacetic	Cases(n)	24	26	36	24	
	OR (95%CI)	1.00	0.94(0.50,1.78)	1.39(0.76,2.56)	0.77(0.37,1.60)	0.87

Adjusted for: educational level, smoking and total energy; * $p<0.05$

Table 3. Odds ratios (OR) of developing ulcerative colitis according to quartiles of polyphenols intake

		Quartile of Intake				P value for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total Polyphenols	Cases(n)	54	61	66	63	
	OR (95%CI)	1.00	1.46(0.93,2.31)	1.59(0.97,2.61)	1.52(0.88,2.63)	0.16
Flavonoids	Cases(n)	66	43	78	57	
	OR (95%CI)	1.00	0.77(0.49,1.22)	1.43(0.92,2.24)	1.10(0.66,1.86)	0.26
Anthocyanidins	Cases(n)	61	62	53	68	
	OR (95%CI)	1.00	1.15(0.76,1.74)	1.03(0.65,1.62)	1.31(0.82,2.10)	0.36
Flavanols	Cases(n)	60	46	80	58	
	OR (95%CI)	1.00	0.85(0.54,1.35)	1.71(1.09,2.69)*	1.30(0.76,2.20)	0.07
Flavonols	Cases(n)	63	64	53	64	
	OR (95%CI)	1.00	1.10(0.71,1.71)	0.91(0.55,1.50)	1.22(0.73,2.03)	0.63
Flavanones	Cases(n)	66	61	66	51	
	OR (95%CI)	1.00	1.00(0.66,1.52)	1.06(0.70,1.62)	0.79(0.50,1.24)	0.38
Flavones	Cases(n)	62	50	67	65	
	OR (95%CI)	1.00	0.97(0.62,1.51)	1.33(0.85,2.08)	1.37(0.81,2.34)	0.14
Isoflavones	Cases(n)	68	61	61	54	
	OR (95%CI)	1.00	0.91(0.59,1.40)	0.84(0.52,1.37)	0.66(0.37,1.20)	0.19
Lignans	Cases(n)	70	56	48	70	
	OR (95%CI)	1.00	0.82(0.54,1.26)	0.72(0.45,1.15)	0.99(0.58,1.70)	0.75
Stilbenes	Cases(n)	64	53	64	63	
	OR (95%CI)	1.00	0.96(0.62,1.49)	1.16(0.74,1.82)	1.09(0.68,1.75)	0.57
Resveratrol		64	48	67	65	
		1.00	0.79(0.50,1.24)	1.30(0.82,2.04)	1.26(0.75,2.11)	0.32
Phenolic acids	Cases(n)	55	59	60	70	
	OR (95%CI)	1.00	1.17(0.74,1.85)	1.21(0.76,1.94)	1.33(0.81,2.19)	0.28

Hydroxybenzoic acid	Cases(n)	73	49	59	63	
	OR (95%CI)	1.00	0.67(0.43,1.04)	0.83(0.53,1.32)	1.00(0.59,1.58)	0.92
Hydroxycinnamic acid	Cases(n)	52	61	56	75	
	OR (95%CI)	1.00	1.31(0.82,2.07)	1.22(0.75,1.97)	1.60(0.98,2.63)	0.10
Hydroxyphenylacetic	Cases(n)	63	57	55	69	
	OR (95%CI)	1.00	1.01(0.66,1.55)	0.93(0.59,1.46)	1.14(0.72,1.82)	0.67

adjusted for: educational level, smoking and total energy; * $p<0.05$

Table 4. Odds ratios (OR) of developing Crohn's disease according to quartiles of polyphenol intake in ever smokers

Polyphenols		Quartile of Intake				
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value for trend
Total polyphenols	Cases(n)	20	19	9	18	
	OR (95%CI)	1.00	0.73(0.29,1.83)	0.28(0.10,0.84)*	0.56(0.20,1.63)	0.13
Flavonoids total	Cases(n)	22	14	10	20	
	OR (95%CI)	1.00	0.69(0.28,1.70)	0.50(0.18,1.38)	1.14(0.36,3.55)	0.67
Anthocyanidins	Cases(n)	24	13	13	16	
	OR (95%CI)	1.00	0.65(0.26,1.66)	0.51(0.20,1.28)	0.69(0.24,1.96)	0.30
Flavanols	Cases(n)	20	21	5	20	
	OR (95%CI)	1.00	1.35(0.57,3.20)	0.21(0.05,0.82)*	1.82(0.51,6.51)	0.66
Flavonols	Cases(n)	20	18	11	17	
	OR (95%CI)	1.00	1.14(0.46,2.83)	0.89(0.28,2.82)	1.07(0.31,3.65)	0.99
Flavanones	Cases(n)	23	13	12	18	
	OR (95%CI)	1.00	0.33(0.13,0.82) *	0.37(0.13,1.06)	0.40(0.17,0.97) *	0.07
Flavones	Cases(n)	25	19	5	17	
	OR (95%CI)	1.00	0.67(0.28,1.59)	0.15(0.04,0.54) *	0.56(0.20,1.58)	0.07
Isoflavones	Cases(n)	11	10	25	20	
	OR (95%CI)	1.00	0.96(0.32,2.87)	3.69(1.15,11.85) *	2.32(0.66,8.11)	0.12
Lignans	Cases(n)	23	14	14	15	

	OR (95%CI)	1.00	0.52(0.21,1.29)	0.38(0.13,1.12)	0.38(0.12,1.19)	0.06
Stilbenes	Cases(n)	21	18	14	13	
	OR (95%CI)	1.00	1.03(0.43,2.51)	0.66(0.25,1.73)	0.57(0.20,1.64)	0.19
Resveratrol	Cases(n)	25	9	19	13	
	OR (95%CI)	1.00	0.42(0.16,1.13)	0.72(0.30,1.73)	0.39(0.14,1.07)	0.14
Phenolic acids	Cases(n)	14	22	16	14	
	OR (95%CI)	1.00	1.14(0.45,2.89)	0.90(0.33,2.49)	0.71(0.26,1.96)	0.37
Hydroxybenzoic acid	Cases(n)	17	19	14	16	
	OR (95%CI)	1.00	1.28(0.49,3.35)	1.32(0.47,3.74)	1.42(0.39,5.15)	0.58
Hydroxycinnamic acid	Cases(n)	14	22	14	16	
	OR (95%CI)	1.00	1.71(0.67,4.41)	1.00(0.36,2.79)	1.10(0.40,3.01)	0.71
Hydroxyphenylacetic	Cases(n)	14	16	20	16	
	OR (95%CI)	1.00	0.82(0.33,2.04)	1.56(0.64,3.80)	1.01(0.37,2.74)	0.56

adjusted for educational level and total energy; * $p<0.05$

Table 5. Odds ratios (OR) of developing ulcerative colitis and polyphenol intake in ever smokers

Polyphenols		Quartile of Intake				P value for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total polyphenols	Cases(n)	39	38	49	47	
	OR (95%CI)	1.00	1.41(0.76, 2.64)	2.00(1.04,3.85)*	2.04(0.95,4.36)	0.05
Flavonoids total	Cases(n)	49	33	53	38	
	OR (95%CI)	1.00	0.86(0.48,1.55)	1.41(0.79,2.52)	1.23(0.61,2.47)	0.30
Anthocyanidins	Cases(n)	43	44	40	46	
	OR (95%CI)	1:00	1.45(0.83,2.52)	1.37(0.75,2.49)	1.50(0.81,2.78)	0.27
Flavanols	Cases(n)	47	35	52	39	
	OR (95%CI)	1:00	0.89(0.51,1.56)	1.44(0.81,2.57)	1.26(0.64,2.51)	0.26
Flavonols	Cases(n)	49	48	36	40	
	OR (95%CI)	1:00	0.97(0.55,1.74)	0.70(0.36,1.36)	1.06(0.54,2.09)	0.88
Flavanones	Cases(n)	42	46	47	38	
	OR (95%CI)	1:00	1.71(0.97,3.03)	1.33(0.76,2.32)	1.05(0.58,1.91)	0.95
Flavones	Cases(n)	47	31	51	44	
	OR (95%CI)	1:00	0.93(0.52,1.65)	1.55(0.88,2.74)	1.34(0.66,2.72)	0.19
Isoflavones	Cases(n)	47	45	42	39	
	OR (95%CI)	1:00	1.04(0.59,1.80)	0.80(0.43,1.50)	0.55(0.26,1.16)	0.12
Lignans	Cases(n)	50	41	36	46	
	OR (95%CI)	1:00	0.96(0.56,1.65)	0.78(0.43,1.42)	1.00(0.48,2.08)	0.74
Stilbenes	Cases(n)	44	41	45	43	
	OR (95%CI)	1:00	1.08(0.60,1.94)	1.21(0.65,2.25)	0.98(0.52,1.87)	0.99
Resveratrol	Cases(n)	44	38	46	45	
	OR (95%CI)	1:00	0.92(0.51,1.65)	1.37(0.76,2.47)	1.02(0.54,1.90)	0.69

Phenolic acids	Cases(n)	31	43	46	53	
	OR (95%CI)	1:00	1.70(0.88,3.29)	2.11(1.06,4.22)*	2.14(1.03,4.46)*	**0.05**
Hydroxybenzoic acid	Cases(n)	56	36	41	40	
	OR (95%CI)	1:00	0.71(0.41,1.23)	0.78(0.43,1.40)	0.85(0.45,1.61)	0.60
Hydroxycinnamic acid	Cases(n)	28	46	44	55	
	OR (95%CI)	1:00	1.85(0.96,3.56)	2.01(0.99,4.07)	2.35(1.13,4.91) *	0.04*
Hydroxyphenylacetic	Cases(n)	48	41	36	48	
	OR (95%CI)	1:00	0.93(0.53,1.63)	0.61(0.33,1.15)	1.01(0.54,1.88)	0.78

adjusted for educational level and total energy; * $p<0.05$

Supplemental Table 1.Participating Centers and Characteristics of the Cohorts

Centre and country	Size of Cohort	Nature of cohort	No. Cases of Incident CD	No. Cases of Incident UC
United Kingdom				
Norfolk	25,639	Population-based cohort of men and women aged 45–74 yr. Recruited between 1993 and 1997. Cases identified up to June 2004 from follow up questionnaires, in-patient admission data and histopathology records.	11	27
Oxford	50,070	Members of United Kingdom vegetarian societies and readers of health food magazines (78% women), aged 20–80 yr recruited between 1994 and 1999. Cases identified up to May 2004 by follow-up questionnaires.	4	15
Germany				
Heidelberg	25,540	Population-based cohort of men aged 45–65 yr and women aged 35–65 yr. Recruited between 1994 and 1998. Cases identified up to June 2007 from follow-up questionnaires.	9	4
Potsdam	27,548	Population-based cohort, men and women, aged 35–64 yr. Recruited between 1994 and 1998. Cases identified up to April 2007 from follow-up Questionnaires.	4	13
Italy				
Florence	13,583	Population-based cohort, men and women, aged 34–64 yr. Recruitment Between 1993 and 1998. Cases identified from regional database of IBD up to May 2004.	2	8
Ragusa	6403	Population-based cohort, men and women, aged 34–65 yr recruited between 1993 and 1997. Case identified up to end of 2010 from follow-up questionnaires, in-patient admission data and histopathology records.	3	19
Sweden				
Umeå	25,732	Population-based cohort, men and women, aged 30–60 yr. Recruited between 1992 and 1996. Cases identified up to February 2007 from regional database of IBD.	10	15
Malmö	28,098	Population-based cohort, men and women, aged 45–69 yr. Recruited between 1991 and 1996. Cases identified up to October 2003 from regional database of IBD.	11	21
Denmark				
Aarhus and Copenhagen	57,053	Population-based cohort of men and women aged 50–64 yr. Recruited between 1993 and 1997. Cases identified up to July 2007 from national database of IBD	11	40
France				
Regions throughout the country	72,996	Women aged 40–65 yr recruited between 1990 and 1993 who are members of a health insurance scheme for school teachers and co-workers. Cases identified up to April 2008 by follow-up questionnaires.	21	28
The Netherlands				
Amsterdam, Doetinchem, Masstricht, and Utrecht	40092	Men and women, aged 20–70 yr recruited between 1993 and 1997 from the general population of 3 cities (Amsterdam, Doetinchem, and Masstricht) and also the breast cancer screening program in Utrecht. Cases identified up to December 2009 by regional IBD databases	17	41
Greece	28,572	Population-based cohort of men and women aged 29–76 yr recruited between 1994 and 1999 from 11 regions throughout Greece. Cases identified up to September 2011 from follow-up questionnaires and histopathology records	7	13
Total	401,326		110	244

Supplemental Table 2. Odds ratios (OR) of Crohn's disease according to quartiles of polyphenol intake in non-smokers

Polyphenols		Quartile of Intake				P value for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total polyphenols	Cases(n)	11	11	7	12	
	OR (95%CI)	1:00	0.58(0.15,2.30)	0.21(0.04,1.12)	0.38(0.08,1.95)	0.23
Flavonoids total	Cases(n)	8	9	12	12	
	OR (95%CI)	1:00	1.11(0.29,4.30)	0.90(0.20,4.03)	1.20(0.21,6.72)	0.94
Anthocyanidins	Cases(n)	10	12	7	12	
	OR (95%CI)	1:00	1.18(0.33,4.28)	0.93(0.24,3.65)	1.09(0.24,4.91)	0.98
Flavanols	Cases(n)	7	9	13	12	
	OR (95%CI)	1:00	1.04(0.25,4.36)	1.08(0.24,4.88)	1.19(0.20,7.11)	0.84
Flavonols	Cases(n)	10	7	10	14	
	OR (95%CI)	1:00	0.86(0.21,3.46)	1.07(0.27,4.22)	1.72(0.39,7.61)	0.46
Flavanones	Cases(n)	14	11	10	6	
	OR (95%CI)	1:00	2.07(0.53,8.10)	1.15(0.32,4.08)	0.97(0.30,3.12)	0.80
Flavones	Cases(n)	11	13	7	10	
	OR (95%CI)	1:00	0.97(0.30,3.10)	0.59(0.17,2.10)	0.72(0.19,2.71)	0.47
Isoflavones	Cases(n)	10	10	13	8	
	OR (95%CI)	1:00	1.19(0.37,3.86)	1.83(0.45,7.43)	1.55(0.35,6.79)	0.46
Lignans	Cases(n)	13	4	13	11	
	OR (95%CI)	1:00	0.06(0.01,0.39)	0.41(0.13,1.35)	0.25(0.06,1.10)	0.41
Stilbenes	Cases(n)	10	12	11	8	
	OR (95%CI)	1:00	1.77(0.50,6.29)	1.27(0.34,4.71)	0.58(0.12,2.78)	0.38
Resveratrol	Cases(n)	13	10	10	8	
	OR (95%CI)	1:00	0.60(0.16,2.19)	0.46(0.11,1.98)	0.32(0.07,1.43)	0.14

Phenolic acids	Cases(n)	10	9	12	10	
	OR (95%CI)	1:00	1.07(0.30,3.80)	0.85(0.27,2.71)	0.87(0.23,3.30)	0.76
Hydroxybenzoic acid	Cases(n)	12	6	10	13	
	OR (95%CI)	1:00	**0.15(0.02,0.96)***	0.22(0.03,1.46)	0.38(0.05,2.81)	0.91
Hydroxycinnamic acid	Cases(n)	11	9	12	9	
	OR (95%CI)	1:00	0.76(0.22,2.60)	0.96(0.35,2.65)	0.57(0.15,2.20)	0.56
Hydroxyphenylacetic	Cases(n)	10	9	15	7	
	OR (95%CI)	1:00	0.92(0.25,3.47)	1.55(0.49,4.95)	0.49(0.09,2.54)	0.77

adjusted for: educational level and total energy; * $p<0.05$

Supplemental Table 3. Odds ratios (OR) of ulcerative colitis according to quartiles of polyphenol intake in non-smokers

Polyphenols		Quartile of Intake				P value for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Total polyphenols	Cases(n)	14	22	15	14	
	OR (95%CI)	1:00	1.79(0.68,4.71)	0.95(0.29,3.07)	0.97(0.30,3.09)	0.56
Flavonoids total	Cases(n)	15	10	24	16	
	OR (95%CI)	1:00	0.62(0.21,1.86)	1.69(0.60,4.76)	0.91(0.29,2.82)	0.70
Anthocyanidins	Cases(n)	13	18	13	21	
	OR (95%CI)	1:00	0.99(0.37,2.65)	0.72(0.24,2.19)	0.97(0.28,3.31)	0.85
Flavanols	Cases(n)	11	10	28	16	
	OR (95%CI)	1:00	0.97(0.30,3.08)	2.80(0.93,8.47)	1.45(0.40,5.29)	0.22
Flavonols	Cases(n)	12	15	16	22	
	OR (95%CI)	1:00	1.11(0.36,3.44)	1.68(0.55,5.12)	2.42(0.74,7.98)	0.08
Flavanones	Cases(n)	22	14	18	11	
	OR (95%CI)	1:00	0.77(0.30,1.94)	0.85(0.33,2.16)	0.61(0.23,1.65)	0.39
Flavones	Cases(n)	13	18	14	20	
	OR (95%CI)	1:00	1.77(0.55,5.75)	0.82(0.25,2.71)	1.99(0.56,7.13)	0.64
Isoflavones	Cases(n)	18	16	17	14	
	OR (95%CI)	1:00	0.60(0.21,1.76)	0.48(0.12,1.91)	0.17(0.03,1.05)	0.07
Lignans	Cases(n)	18	13	11	23	
	OR (95%CI)	1:00	0.44(0.17,1.13)	0.23(0.07,0.71)	0.71(0.26,1.96)	0.58
Stilbenes	Cases(n)	17	10	18	20	
	OR (95%CI)	1:00	0.50(0.20,1.30)	0.97(0.36,2.64)	0.82(0.28,2.40)	0.97
Resveratrol	Cases(n)	16	9	20	20	
	OR (95%CI)	1:00	0.59(0.20,1.75)	1.08(0.41,2.88)	0.90(0.31,2.59)	0.97
Phenolic acids	Cases(n)	23	14	14	14	

	OR (95%CI)	1:00	0.55(0.22,1.34)	0.70(0.27,1.80)	0.57(0.21,1.56)	0.35
Hydroxybenzoic acid	Cases(n)	15	11	18	21	
	OR (95%CI)	1:00	0.59(0.20,1.79)	1.26(0.40,3.96)	1.87(0.65,5.40)	0.16
Hydroxycinnamic acid	Cases(n)	22	14	12	17	
	OR (95%CI)	1:00	0.63(0.24,1.63)	0.65(0.25,1.69)	0.82(0.33,2.06)	0.65
Hydroxyphenylacetic	Cases(n)	13	14	19	19	
	OR (95%CI)	1:00	0.79(0.29,2.13)	1.30(0.50,3.37)	0.97(0.37,2.55)	0.78

adjusted for: educational level and total energy; * $p<0.05$