Published in final edited form as:

Eur J Cancer Prev. 2011 March ; 20(2): 86–95. doi:10.1097/CEJ.0b013e3283429e45.

Do Interleukin Polymorphisms Play a Role in the Prevention of Colorectal Adenoma Recurrence by Dietary Flavonols?

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Abstract

Chemopreventive dietary compounds, such as flavonols, may inhibit colorectal carcinogenesis partly by altering cytokine expression and attenuating inflammation. Single nucleotide polymorphisms (SNPs) in the promoter regions of genes encoding cytokines may influence flavonol-induced changes in cytokine expression and consequently cancer risk. Using logistic regression, we estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between SNPs of interleukin (IL)-1 β , 6, 8, and 10, alone or combined with flavonol intake or serum IL concentration changes, and adenoma recurrence in 808 participants from the intervention arm of the Polyp Prevention Trial, a 4-year intervention study evaluating the effectiveness of a low-fat, high-fiber, high-fruit and vegetable diet on adenoma recurrence. Overall, SNPs in genes encoding IL-1 β , 6, 8, and 10 were not associated with their corresponding serum concentrations or adenoma recurrence. However, individuals homozygous for *IL-10* -592 C (OR = 2.23, 95% CI: 1.07–4.66, *P* interaction = 0.03) or *IL-10* -819 C (OR = 2.18, 95% CI: 1.05–4.51, *P* interaction = 0.05) had an elevated risk of high risk adenoma recurrence when their serum IL-10 concentrations increased during the trial. In addition, *IL-6* -174 GG in combination with above median flavonol intake (OR = 0.14, 95% CI: 0.03–0.66) or with decreased IL 6 concentrations (OR = 0.14, 95% CI: 0.03–0.65) reduced the risk of advanced adenoma recurrence, although the interaction term was not statistically significant. In conclusion, our results suggest that IL SNPs, in combination with a flavonol-rich diet or decreased serum IL, may lower the risk of adenoma recurrence.

Keywords

adenoma recurrence; flavonols; interleukins

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Conflict of interest: None

INTRODUCTION

Flavonols are a group of bioactive polyphenols that are abundant in some fruits, vegetables, and tea [1–2]. In the U.S., the median flavonol intake is estimated to be approximately 10–12 mg/d with a range between 0 and 40 mg (Peterson JJ, personal communication). We reported that daily consumption of dietary flavonols above 30 mg decreases the risk of advanced and high risk colorectal adenoma recurrence [3]. Flavonols may impede growth of colorectal neoplasms by their anti-oxidative [4], anti-mutagenic [5], anti-proliferative [6], anti-inflammatory [7–9], and anti-cell transformation properties [10] as well as by inducing apoptosis [11], and inhibiting matrix metalloproteinases and angiogenesis [12–13]. We are especially interested in the anti-inflammatory properties of flavonols for cancer prevention, as flavonols may attenuate the secretion of the pro-inflammatory and pro-carcinogenic cytokines interleukin (IL) 1 β , 6, 8 [14–16;8;17–18] and inhibit the secretion of the pro- and anti-carcinogenic IL-10 [19;15].

We reported that increases in serum IL-1 β , IL-6, and IL-10 are potential indicators of advanced adenoma recurrence; moreover, that a decrease in these serum cytokines in conjunction with flavonol consumption above 30 mg/d indicated an even lower risk of advanced adenoma recurrence [3](Bobe et al., in press). Single-nucleotide polymorphisms (SNPs) in the promoter region of genes encoding IL-1 β , IL-6, IL-8, and IL-10 may alter the secretion of cytokines [20–24] and, as a result, the risk of adenoma recurrence generally or in response to dietary flavonols. Thus, IL SNPs may indicate individuals more likely to benefit from a chemopreventive dietary intervention.

The aim of this study was to examine whether SNPs in the promoter regions of genes encoding IL-1 β , 6, 8, and 10 could influence, alone or in combination with flavonol intake or serum IL concentrations, adenoma recurrence. To our knowledge, this is the first study to investigate the joint effects of IL genotype, serum IL levels, and flavonol intake on adenoma recurrence.

MATERIALS AND METHODS

Study Design and Population

The Polyp Prevention Trial (PPT) was a large, multi-center, randomized 4-year nutritional intervention trial to evaluate the effects of promoting a high fiber, high-fruit and vegetable, low-fat diet on the recurrence of colorectal adenomas. Details of the study have been described elsewhere [25–27]. In brief, study participants had at least one histologically confirmed colorectal adenoma identified by complete colonoscopy in the six months prior to study entry. Of the 1,905 participants who completed the trial by undergoing a colonoscopy at the end of year four, 958 were in the intervention arm. Our study included the 808 participants in the intervention arm with available dietary data for any of the first 3 years of the trial, IL-SNP data, and serum from baseline (T0) and from either year 1 (T1) or 3 (T3). Dietary information and serum samples from T4 were not used because some of these were taken after the final colonoscopy. All lesions were examined for histological features and degree of atypia by two independent pathologists. Recurrence outcomes were defined as having any (n = 318), advanced (≥ 1 adenoma of ≥ 1 cm in size, having at least 25% villous component, or exhibiting high-grade dysplasia; n = 45) or high risk (≥ 1 advanced adenoma or ≥ 3 pathologically confirmed adenomas; n = 88) adenomas.

Lifestyle and Flavonol Data

Participants completed an interviewer-administered questionnaire regarding demographics, family history, and use of medication or supplements at baseline (T0) and at each of the annual follow-up visits (T1, T2, T3, T4). A modified food frequency questionnaire (FFQ)

eliciting information on the frequency and portion size of 119 food and beverage items consumed over the past 12 months [28–29] was also completed at each of these visits. Trained, certified nutritionists reviewed all FFQs with participants. Using the 2007 U.S. Department of Agriculture (USDA) flavonoid database that contains flavonol values for 308 food and beverage items [30], 55 of the 119 food and beverage items could be matched with flavonol values, which were provided as concentrations of the individual flavonols isorhamnetin, kaempferol, myricetin, and quercetin. Flavonol intake was calculated as the sum of isorhamnetin, kaempferol, myricetin, and quercetin, which represent over 99% of dietary flavonol intake [1–2]. Compared with 24-hr dietary recall and four-day food record data, the FFQ slightly overestimated fat and underestimated fiber, fruit & vegetable intake and had acceptable correlations of fat ($r = 0.63$), fiber ($r = 0.63$), fruit & vegetable ($r = 0.72$), dry bean ($r = 0.76$), and other macro- and micronutrients [29;27].

Interleukin Genotype Data

The SNPs in IL-encoding genes were selected based on the following criteria: (i) a reported association between the SNP and colorectal adenoma or cancer [31–35], (ii) an association between the SNP and transcriptional activity and serum concentrations of its encoded gene product [20–24], and (iii) evidence that flavonols alter the activities of transcription factors of IL-encoding genes [36;6;10;37] and serum concentrations of their gene product [38–39;18]. Details of the genotyping have been previously described [40]. In brief, high-throughput genotyping was carried out by BioServe Biotechnologies, Ltd. (Laurel, MD) using a two-step PCR process and mass spectrometry (Masscode, Qiagen Genomics, Bothell, WA) [41]. Call rates for SNPs in IL-encoding genes were as follows: *IL-1 β* -511 C>T (rs16944) 93.5%, *IL-6* -174 G>C (rs1800795) 91.8%, *IL-8* -251 T>A (rs4073) 92.7%, *IL10* -592 C>A (rs1800872) 98.3%, *IL10* -819 C>T (rs1800871) 95.0%, and *IL-10* -1082 G>A (rs1800896) 95.5%. Quality control consisted of repeated assays of approximately 10% randomly selected samples as well as the inclusion of blinded controls. The concordance of duplicate samples was above 97%.

Interleukin Serum Data

Serum concentrations of IL-1 β , IL-6, IL-8, and IL-10 at baseline, T1, and T3 were measured by the Clinical Support Laboratory of SAIC Frederick, Inc. (Frederick, MD) using a commercially available multiplex 96-well enzyme-linked immunoabsorbent assay kit (MS6000 Human Pro-Inflammatory 9-Plex Ultra-Sensitive Kit K11007; Meso Scale Diagnostics, Gaithersburg, MD) on a Sector™ Imager 6000 according to the manufacturer's recommendation (Meso Scale Diagnostics, Gaithersburg, MD). The interassay coefficients of variation (CVs) were below 15%.

Statistical Analyses

Statistical analyses were performed using SAS, version 9.1 (SAS, Inc., Cary, North Carolina) software. Baseline characteristics, average dietary intake for the first 3 years of the trial, and serum IL concentrations were evaluated by adenoma recurrence at T4 (no vs. any, high risk, or advanced adenoma recurrence) using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables and are shown as medians and interquartile ranges (IQRs). All SNPs were tested for, and were in agreement with, Hardy-Weinberg equilibrium.

The associations between IL SNPs and their corresponding serum concentrations were evaluated with the Kruskal Wallis test and multiple linear regression models. Potential confounders, listed in Table 1, were included in the logistic regression models if the confounder changed the association by 10% or more, was associated with both IL SNPs and their corresponding serum concentrations, and had a χ^2 P value ≤ 0.20 . Regular nonsteroidal

anti-inflammatory drug (NSAID) use was not included in the statistical models because it was not associated with adenoma recurrence in this population (Table 1) [42;3].

We used logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI) for adenoma recurrence at T4 by IL SNPs, using the homozygote of the more frequent allele as the referent category and race, age, and gender as covariates. For linear trend testing, the referent category was the more frequent allele which was scored on an ordinal scale as 0, the heterozygote was scored as 1, and the rare homozygote was scored as 2 (co-dominant model). For the dominant model, homozygous and heterozygous carriers of the less frequent gene were combined and scored as one. The IL-10 haplotypes were composed of 3 polymorphic sites -1082 A/G, -819 C/T, and -592 C/A: *IL-10 A-C-C* was comprised of -1082 AA, -819 CC, -592 CC (referent haplotype); *IL-10 G-C-C* being -1082 G, -819 CC, -592 CC; and *IL-10 G-T-A* being -1082 G, -819 T, -592 A.

The combined effect of IL genotype and flavonol intake on colorectal adenoma recurrence was evaluated using the median flavonol intake during the first 3 years of the trial as the cut-point ($\leq$ median, $>$ median) and carrier status of the rare allele (yes, no). The group with the largest number of advanced adenoma cases was chosen as the referent category consisting of individuals with below median flavonol intake, who carried at least one copy of the less frequent allele. To examine the combined effect of IL genotype and changes in serum IL-concentrations, defined as the geometric mean of T1 and T3 minus the baseline values, we used the median IL change as the cut-point ($\leq$ median, $>$ median); the referent category was individuals with an increase in IL concentrations, who carried at least one copy of the less frequent allele. Effect modification was evaluated by calculating the cross product interaction terms. All p values corresponded to two-sided tests. Differences were considered to be significant at $P \leq 0.05$ and borderline significant at $0.05 < P \leq 0.10$.

RESULTS

At the end of the 4-year trial, 39% of the 808 participants in the intervention arm had 1 or more adenoma, 11% had a high risk adenoma, and 6% had an advanced adenoma (Table 1). Adenoma recurrence was more common in older individuals. Flavonol consumption doubled from 14.6 mg/d at baseline to 29.7 mg/d during the first 3 years of the trial [3]. Those with any adenoma recurrence consumed more flavonols at baseline. Individuals with high risk and advanced adenoma recurrence ate more calories from fat and consumed less fruits & vegetables, fiber, flavonols, and dry beans during the first 3 years of the study. High risk adenoma recurrence was also positively associated with BMI.

The SNPs in genes encoding IL-1 β , IL-6, IL-8, and IL-10 were not associated with serum concentrations of their gene product; however, baseline serum IL-10 concentrations tended to linearly increase with *IL-10 -819 T* allele copy number ($P_{\text{for trend}} = 0.07$) and *IL-10 G-T-A* haplotype ($P_{\text{for trend}} = 0.06$) (Table 2). Furthermore, an exploratory analysis suggested that IL SNPs may alter serum concentrations of ILs other than their own gene product, for example *IL-1 β -511* SNP was associated with serum IL-8, *IL-8 -251* SNP was associated with serum IL-6, and *IL-10 -592* SNP was associated with serum IL-1 β (results not shown).

Alone, the examined IL SNPs did not predict risk of adenoma recurrence in either a dominant or co-dominant model; except that the *IL-1 β -511 T* and the *IL-6 -174 G* alleles may have a protective effect against high risk (OR = 0.62; 95% CI: 0.38–1.01; $P = 0.05$ for the dominant model) and advanced adenoma recurrence ($P_{\text{for trend}} = 0.07$ for the co-dominant model), respectively (Table 3).

We investigated whether IL SNPs in combination with changes in serum IL concentrations during the trial may affect risk of adenoma recurrence (Table 4). The analysis is based on

the widespread assumption that SNPs will only be able to affect adenoma risk if they are functionally significant, meaning that they can alter secretion of their gene products, which is in this case IL secretion. An increase in serum IL-10 resulted in a greater risk of high risk adenoma recurrence when combined with *IL-10* -592 CC (OR = 2.23, 95% CI: 1.07–4.66; $P = 0.03$ compared with individuals carrying the A allele; $P_{Interaction} = 0.03$) or with *IL-10* -819 CC (OR = 2.18, 95% CI: 1.05–4.51; $P = 0.04$; compared with individuals carrying the T allele; $P_{Interaction} = 0.05$). In addition, individuals with the combination of *IL-6* -174 GG and a decrease in serum IL-6 had a statistically significantly lower risk of advanced adenoma recurrence compared to those with each of the other 3 combinations of *IL-6* -174 SNP and serum IL-6 change ($P_{Interaction} = 0.06$).

When IL SNPs were analyzed with flavonol intake (Table 5), individuals that carried *IL-6* -174 GG and had above median flavonol consumption had a statistically significantly lower risk of advanced adenoma recurrence compared to each of the other 3 combinations of *IL-6* -174 SNP and flavonol intake; however, the interaction term was, in contrast to the main effects for *IL-6* SNP ($P = 0.05$) and flavonol intake ($P = 0.04$), not significant ($P = 0.16$). Furthermore, those with above median flavonol intake combined with the *IL-1β* -511 T allele (OR = 0.32, 95% CI: 0.11–0.94; $P = 0.04$), *IL-10* -592 A allele (OR = 0.17, 95% CI: 0.04–0.80; $P = 0.02$), or *IL-10* -819 T allele (OR = 0.18, 95% CI: 0.04–0.84; $P = 0.03$) had a lower risk of advanced adenoma recurrence compared with individuals of the same genotype and below or median flavonol intake (Table 5).

DISCUSSION

Our objective was to examine whether SNPs in the promoter region of genes encoding IL-1β, IL-6, IL-8, and IL-10 may influence, alone or in combination with flavonol intake or serum IL concentrations, adenoma recurrence. Overall, we found no statistically significant associations between the SNPs in IL-encoding genes and serum concentrations of their gene products or colorectal adenoma recurrence in the intervention arm of the PPT, suggesting that IL SNPs alone may not predict adenoma recurrence. However, individuals homozygous for *IL-10* -592 C or *IL-10* -819 C had an elevated risk of high risk adenoma recurrence when their serum IL-10 concentrations increased during the trial. In addition, *IL-6* -174 GG in combination with above median flavonol consumption or with decreases in serum IL-6 concentrations during the trial resulted in a reduced risk of advanced adenoma recurrence. Our results suggest that IL SNPs, in combination with flavonol intake or serum IL concentrations, may influence adenoma recurrence.

Growing evidence suggests that chronic inflammation, involving upregulation of both pro- and anti-inflammatory ILs, may be an important target for colorectal cancer prevention [15]. Gene and protein expression of IL-1β, IL-6, and IL-8 is elevated in the tumor microenvironment compared to normal colon tissue [43], often indicated by an increase in serum IL-1β, IL-6, and IL-10 concentrations in individuals with advanced adenoma recurrence [3](Bobe et al., in press). Thus, functional SNPs in the promoter regions of genes encoding IL-1β, IL-6, IL-8, and IL-10 may alter secretion of ILs [20–24] and, as a result, cancer risk [44]. Consistent with previous studies [40;45], we found IL SNPs alone did not predict adenoma recurrence. In previous studies, the direction of associations between IL-1β, IL-6, IL-8, and IL-10 SNPs and colorectal adenoma [31] or cancer [32;46;33;47;34–35;48] have been inconsistent.

SNPs in the promoter regions of ILs are one of many mechanisms by which IL secretion, inflammation, and further downstream colorectal neoplastic changes can be altered. Besides SNPs, IL gene and protein expression can be changed by epigenetic events, abundance and distribution of nuclear transcription factors, micro RNAs, the half-life of mRNA transcripts,

and other post-transcriptional mechanisms [49–50]. Environmental factors, inflammation status, and IL induction model modify IL gene and protein expression [20–24]. Serum IL concentration measurements may not necessarily indicate true physiological IL bioavailability because serum IL concentrations are generally low, have a limited dynamic range, diurnal variations, and short half-lives, and lack specificity for location, strength and type of inflammation. Furthermore, the influence of IL SNPs on inflammation and cancer may be more complex than a direct association between IL SNPs and serum concentrations of their gene product (in our exploratory analysis, IL SNPs were associated with serum concentrations of ILs other than their gene product).

An increase in serum IL concentrations in combination with a specific IL genotype may indicate increased risk of adenoma recurrence. In this study, individuals with *IL-10* -592 CC or *IL-10* -891 CC had the greatest risk of high risk adenoma recurrence when their serum IL-10 concentrations increased during the trial. The role of IL-10 in colorectal carcinogenesis is complex [15]: IL-10 may promote or inhibit colorectal neoplastic changes depending on environmental factors such as the intestinal microbial population in the host. Elevated serum IL-10 may indicate down-regulation or up-regulation of inflammation, as IL-10 secretion is up-regulated in response to increased inflammation. Smoking, nuclear transcription factors, BMI, gender, regular NSAID use, and other IL-10 SNPs may partly determine which IL-10 allele up-regulates IL-10 gene and protein expression more strongly [51–52;22;53]. This may explain why IL-10 SNPs are not consistently associated with increased risk of colorectal cancer [33–35] indicating a complex interaction between environmental factors, IL-10 SNPs, inflammation, and colorectal cancer.

Host genetics may partly predict whether dietary bioactive compounds have chemopreventive properties. Part of the chemoprotective effect of flavonols may involve attenuating secretion of pro-inflammatory compounds [6;10;18], which, in part, may be regulated by SNPs in the promoter region of ILs. In support of our hypothesis, individuals with *IL-6* -174 GG, in combination with higher flavonol intake, had a decreased risk of advanced adenoma recurrence compared to other combinations of flavonol consumption and *IL-6* -174 SNP, although this observation is based on very few cases. The role of *IL-6* -174 SNP on prevention of adenoma recurrence is not surprising given that the *IL-6* -174 SNP is close to binding sites of IL-6 transcription factors [50;54] that can be modified by flavonols [36;10] and the fact that high flavonol intake (>30 mg/d) decreased serum IL-6 concentrations and high risk and advanced adenoma recurrence in the PPT [3].

A major strength of this study is the information on adenomas from complete colonoscopies performed at baseline, T1, and T4, as well as histologic characteristics noted by two pathologists independently, decreasing the risk of misclassification. Another strength is that the dietary questionnaire, developed specifically for this study, focused on fruit & vegetable consumption [28–29;27], and the questionnaire was linked to the recently released validated USDA flavonoid database [30]. Furthermore, registered dietitians reviewed the completed dietary questionnaires with participants, which further improved the accuracy of the questionnaire [29;27]. Other strengths of this study included the prospective and repeated collection of both the serum and dietary data.

There are, however, several limitations to our study. Our study findings may not apply to the general population because all participants had a history of adenomas, a relative healthy diet, and most engaged in a health-promoting lifestyle. The observed associations could be due to chance, multiple comparisons, or to IL SNP being in linkage disequilibrium with other functional or regulatory SNPs [23]. Dietary measurement error related to the dietary assessment technique cannot be ruled out and could lead to attenuated risk estimates. The dietary intervention of the trial was not specific to flavonol consumption; therefore,

observed changes could be the result of other chemoprotective compounds known to decrease colorectal adenoma risk, such as dry beans, fiber, and folate. However, none of the other chemopreventive compounds had a significant effect on adenoma recurrence in the PPT, except for dry beans, which have a high flavonol content. Furthermore, we had limited statistical power for testing interactions between IL SNPs, flavonol intake, serum IL concentrations, and advanced adenoma recurrence. However, this is, to our knowledge, the first study to investigate the joint effects of IL genotype, serum IL levels, and flavonol intake on adenoma recurrence.

In conclusion, our results suggest that IL SNPs, in combination with a flavonol-rich diet or with a decrease in serum IL concentrations, may decrease the risk of adenoma recurrence. Further studies are needed to examine the importance and biological role of IL SNPs for chemopreventive strategies to identify individuals more likely to benefit from chemopreventive compounds such as flavonols.

Acknowledgments

We would like to thank the Polyp Prevention Trial Study Group for their outstanding contribution to this project. The authors thank Helen Rager and Yanyu Wang from the Clinical Support Laboratory of SAIC Frederick, Inc. (Frederick, MD) for cytokine analysis of the serum samples.

Funding: This study was funded by the Office of Dietary Supplements (OD-08-007) and the Intramural Research Program, National Cancer Institute, NIH, Bethesda, MD.

Abbreviations

BMI	body mass index
CI	confidence interval
CV	coefficient of variation
FFQ	food frequency questionnaire
IL	interleukin
IQR	interquartile range
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PPT	Polyp Prevention Trial
SNP	single nucleotide polymorphism

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Appendix

The members of the Polyp Prevention Study Group participated in the conduct of the Polyp Prevention Trial. However, the data presented in this manuscript and the conclusions drawn from them are solely the responsibility of the above listed coauthors.

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Table 1

Proportions and medians (interquartile ranges) of participant characteristics in the intervention arm of the Polyp Prevention Trial by adenoma recurrence at T4 (n = 808)^a

Characteristics	Adenoma Recurrence (T4)					
	None	Any	High Risk		Advanced	
	Median (IQR) or %	Median (IQR) or %	P value [†]	Median (IQR) or %	P value [†]	Median (IQR) or %
Sample size (%)	490 (61)	318 (39)		88 (11)		45 (6)
<u>Baseline (T0):</u>						
Gender (% male)	63	69	0.15	73	0.11	67
Race (% Caucasian)	89	90	0.73	90	0.86	87
Education (% ≤ high school)	23	28	0.13	31	0.14	29
Family history of colorectal cancer (% yes) ^a	27	26	0.94	31	0.52	27
Smoker (% current)	11	13	0.32	16	0.20	13
NSAID use (% yes) ³	36	37	0.82	33	0.63	31
Supplement use (% yes) ^b	45	44	0.77	41	0.49	38
Hormone therapy (% yes) ^b	14	9	0.06	7	0.08	9
Age (y)	60.0 (52.0–67.0)	64.0 (56.0–70.0)	<.0001	66.0 (57.0–71.0)	<.0001	66.0 (57.0–71.0)
Body mass index (kg/m ²)	27.5 (25.0–30.1)	27.4 (25.1–30.3)	0.78	28.3 (25.6–31.1)	0.06	29.4 (26.7–32.4)
Physical activity (hr/wk) ^c	8.50 (4.00–15.8)	8.38 (3.85–15.7)	0.72	8.27 (3.33–12.6)	0.22	5.75 (1.94–12.0)
Dietary flavonols (mg/d)	13.9 (9.32–20.8)	15.7 (10.1–22.9)	0.03	13.8 (9.23–19.9)	0.76	12.2 (8.00–18.1)
<u>Serum cytokines (in pg/mL):</u>						
Interleukin 1β	0.36 (0.22–0.60)	0.36 (0.22–0.63)	0.89	0.37 (0.21–0.71)	0.93	0.34 (0.19–0.62)
Interleukin 6	1.88 (1.35–2.80)	1.89 (1.36–2.75)	0.83	1.97 (1.43–2.68)	0.39	1.77 (1.41–2.62)
Interleukin 8	10.5 (7.87–14.0)	10.3 (8.09–14.3)	0.60	11.1 (8.47–16.8)	0.12	11.4 (8.79–15.8)
Interleukin 10	3.27 (2.16–5.68)	3.28 (2.12–6.27)	0.93	3.23 (2.22–4.62)	0.47	2.80 (2.03–4.18)
<u>Trial (T1,2,3,4):</u>						
<u>Dietary intake:</u>						
Alcohol (g/d)	0.91 (0.00–8.49)	0.96 (0.00–8.05)	0.54	0.99 (0.00–5.80)	0.64	0.54 (0.00–4.93)
Energy (1,000 kcal/d)	1.77 (1.52–2.06)	1.80 (1.54–2.07)	0.80	1.82 (1.56–2.00)	0.91	1.82 (1.57–1.99)
Fat (% kcal/d)	22.4 (18.5–26.5)	22.6 (19.6–27.8)	0.11	23.5 (20.5–29.5)	0.007	26.9 (21.2–30.6)
						0.001

Characteristics	Adenoma Recurrence (T4)					
	None		Any		Advanced	
	Median (IQR) or %	P value [†]	Median (IQR) or %	P value [†]	Median (IQR) or %	P value [†]
Fiber (g/d)	32.2 (24.3–41.1)	0.17	31.0 (23.2–39.0)	0.03	29.4 (20.4–37.7)	0.05
Fruits & vegetables (servings/d)	5.72 (4.43–7.20)	0.71	5.69 (4.51–7.01)	0.05	4.93 (4.04–6.03)	0.01
Flavonols (mg/d)	29.6 (21.2–40.5)	0.74	29.7 (21.1–38.9)	0.02	20.6 (14.9–30.8)	0.0004
Dry beans(g/d)	31.2 (15.4–56.2)	0.26	30.4 (14.5–49.5)	0.01	14.0 (7.37–37.5)	0.0004
<i>Serum cytokines (in pg/mL):</i>						
Interleukin 1β	0.36 (0.24–0.64)	0.43	0.36 (0.23–0.58)	0.40	0.43 (0.25–0.71)	0.32
Interleukin 6	1.96 (1.44–2.77)	0.39	2.01 (1.53–2.80)	0.01	2.07 (1.66–3.07)	0.15
Interleukin 8	10.7 (8.18–15.5)	0.70	10.9 (8.28–14.7)	0.88	11.5 (8.78–17.1)	0.38
Interleukin 10	3.20 (2.21–5.53)	0.77	3.21 (2.31–5.98)	0.59	3.21 (1.87–5.77)	0.64

* Participant characteristics stratified by adenoma recurrence have been previously presented for 872 participants from the intervention arm of the Polyp Prevention Trial [3][Bobe et al., in press].

[†] All comparisons against the no adenoma recurrence group. P values for differences in proportions were calculated using Fisher's exact test. P values for differences in medians were calculated using Wilcoxon rank-sum test.

^a Family history of colorectal cancer was defined as having ≥ 1 first-degree relative with colorectal cancer at baseline.

^b Regular non-steroidal anti-inflammatory drug (NSAID) use, hormone therapy, and supplement use were tested at baseline and use throughout the first 3 trial years. Regular dietary supplement use was defined as taking supplement ≥ 1 weekly. Regular medication use, including NSAIDs, was defined as taking medication ≥ 1 monthly. Hormone replacement therapy included both unopposed estrogen and estrogen/progestin combinations.

^c Physical activity was defined as self-reported time typically spent for any type of moderate or vigorous physical activity.

^d T1,2,3: mean values of the first three years of the trial for dietary variables and geometric mean of year 1 and 3 cytokine values.

Medians (interquartile ranges; in pg/mL) of serum interleukin concentrations in the intervention arm of the Polyp Prevention Trial by their corresponding interleukin polymorphism (n = 808)

Table 2

Interleukin	Interleukin Concentrations (Median, IQR in pg/mL)			P Non	P for
Polymorphism	C/C	C/T	T/T	Param. *	Trend [†]
<i>IL-1β -511</i>					
Sample size	319	359	78		
Baseline (T0)	0.35 (0.22–0.63)	0.37 (0.22–0.59)	0.38 (0.21–0.74)	0.93	0.40
Intervention (T1,3)	0.36 (0.23–0.59)	0.38 (0.24–0.65)	0.37 (0.25–0.61)	0.74	0.82
Change (T1,3–T0)	–.01 (–0.15–0.14)	0.02 (–0.11–0.16)	0.03 (–0.11–0.21)	0.19	0.75
<i>IL-6 -174</i>					
Sample size	284	353	105		
Baseline (T0)	1.83 (1.27–2.95)	1.89 (1.36–2.72)	2.03 (1.44–2.84)	0.62	0.40
Intervention (T1,3)	1.95 (1.44–2.88)	2.00 (1.44–2.80)	1.90 (1.49–2.54)	0.85	0.82
Change (T1,3–T0)	0.02 (–0.44–0.55)	0.11 (–0.35–0.50)	–.01 (–0.70–0.54)	0.52	0.72
<i>IL-8 -251</i>					
Sample size	187	378	179		
Baseline (T0)	10.6 (7.95–13.5)	10.4 (7.88–14.1)	10.7 (8.05–14.9)	0.63	0.23
Intervention (T1,3)	11.2 (8.39–15.7)	10.5 (7.93–15.1)	10.9 (8.41–16.2)	0.38	0.45
Change (T1,3–T0)	0.50 (–2.17–3.08)	0.19 (–2.09–2.38)	0.49 (–1.73–2.82)	0.67	0.75
<i>IL-10 -592</i>					
Sample size	432	275	62		
Baseline (T0)	3.16 (2.07–5.59)	3.36 (2.20–6.48)	3.35 (1.96–4.89)	0.53	0.16
Intervention (T1,3)	3.18 (2.09–5.59)	3.31 (2.14–5.66)	3.08 (2.25–5.33)	0.80	0.26
Change (T1,3–T0)	–.03 (–0.82–0.56)	–.16 (–0.96–0.50)	0.04 (–0.49–0.83)	0.14	0.29
<i>IL-10 -819</i>					
Sample size	444	279	66		
Baseline (T0)	3.14 (2.09–5.51)	3.42 (2.21–6.71)	3.35 (1.98–4.89)	0.29	0.07
Intervention (T1,3)	3.13 (2.13–5.55)	3.34 (2.23–5.66)	3.02 (2.22–5.23)	0.72	0.24

Interleukin	Interleukin Concentrations (Median, IQR in pg/mL)			P Non	P for
Polymorphism				Param. *	Trend†
Change (T1,3-T0)	0.00 (−0.82–0.58)	−.12 (−0.96–0.49)	0.00 (−0.64–0.60)	0.26	0.29
<i>IL-10 -1082</i>					
Sample size	A/A 221	A/G 409	G/G 147		
Baseline (T0)	3.24 (2.02–5.94)	3.44 (2.24–6.18)	3.24 (2.02–5.27)	0.29	0.29
Intervention (T1,3)	3.04 (2.15–5.58)	3.35 (2.25–5.86)	2.97 (2.00–5.09)	0.46	0.17
Change (T1,3-T0)	−.03 (−0.70–0.60)	−.07 (−1.01–0.58)	−.05 (−0.83–0.46)	0.56	0.09
<i>IL-10 Haplotype^a</i>					
Sample size	A-C-C 143	G-C-C 269	G-T-A 322		
Baseline (T0)	3.32 (2.01–5.27)	3.18 (2.15–5.69)	3.39 (2.18–6.48)	0.38	0.06
Intervention (T1,3)	3.26 (2.35–5.78)	3.31 (2.23–5.78)	3.16 (2.01–4.88)	0.53	0.16
Change (T1,3-T0)	−.05 (−0.81–0.51)	−.03 (−0.93–0.62)	−.09 (−0.93–0.56)	0.81	0.20

* P values for differences in medians among the flavonol intake quartiles were calculated based on the Kruskal-Wallis test.

† Median concentrations of each interleukin genotype were used to determine P for trend of the interleukin concentrations using a multiple regression model adjusting for age tertiles (<58, 58–66, >66 yrs), sex, race (Caucasian, non Caucasian), average BMI (<25, 25.0–29.9, ≥30 kg/m²), and current smoking status during the first 3 trial years.

^a Composed of 3 polymorphic sites: -1082 AA/G, -819 CC/T, and -592 CC/A.

Association between interleukin polymorphisms and colorectal adenoma recurrence in participants of the Polyp Prevention Trial at the end of Year 4 (n = 808)

Table 3

Interleukin	Adenoma Recurrence					
	None	Any	High Risk		Advanced	
Polymorphism	n (%)	n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	n (%)
<i>IL-1β -511</i>						
C/C	190 (59.6)	129 (40.4)	1.00	43 (13.5)	1.00	19 (6.0)
C/T	222 (61.8)	137 (38.2)	0.90 (0.66–1.24)	32 (8.8)	0.61 (0.36–1.01)	18 (5.0)
T/T	50 (61.1)	28 (35.9)	0.83 (0.49–1.41)	8 (10.3)	0.68 (0.29–1.57)	4 (5.1)
C/T + T/T	272 (62.2)	165 (37.8)	0.89 (0.66–1.21)	40 (9.2)	0.62 (0.38–1.01)	22 (5.0)
P-trend			0.42		0.11	0.46
<i>IL-6 -174</i>						
G/G	181 (63.7)	103 (36.3)	1.00	30 (10.6)	1.00	13 (4.6)
G/C	208 (58.9)	145 (41.1)	1.25 (0.89–1.75)	45 (12.7)	1.40 (0.82–2.40)	22 (6.2)
C/C	64 (61.0)	41 (39.0)	1.19 (0.74–1.91)	9 (8.6)	1.04 (0.45–2.40)	8 (7.6)
G/C + C/C	272 (59.4)	186 (40.6)	1.24 (0.90–1.71)	54 (11.8)	1.33 (0.79–2.24)	30 (6.6)
P-trend			0.32		0.58	0.07
<i>IL-8 -251</i>						
T/T	118 (63.1)	69 (36.9)	1.00	16 (8.6)	1.00	8 (4.3)
A/T	228 (60.3)	150 (39.7)	1.16 (0.80–1.68)	44 (11.6)	1.45 (0.77–2.71)	23 (6.1)
A/A	112 (62.6)	67 (37.4)	1.03 (0.66–1.60)	16 (8.9)	1.08 (0.50–2.33)	10 (5.6)
A/T + A/A	340 (61.0)	217 (39.0)	1.12 (0.79–1.60)	60 (10.8)	1.34 (0.73–2.45)	33 (5.9)
P-trend			0.87		0.82	0.63
<i>IL-10 -592</i>						
C/C	264 (61.6)	168 (38.9)	1.00	51 (11.8)	1.00	27 (6.3)
C/A	171 (62.2)	104 (37.8)	0.92 (0.67–1.26)	26 (9.5)	0.76 (0.45–1.28)	13 (4.7)
A/A	33 (53.2)	29 (46.8)	1.45 (0.83–2.53)	7 (11.3)	1.17 (0.47–2.90)	3 (4.8)
C/A + A/A	204 (60.5)	133 (39.5)	0.99 (0.74–1.34)	33 (9.8)	0.82 (0.50–1.33)	16 (4.7)
P-trend			0.55		0.68	0.42
<i>IL-10 -819</i>						

Interleukin	Adenoma Recurrence					
	None	Any	High Risk	Advanced		
Polymorphism	n (%)	n (%)	OR (95% CI)*	n (%)	OR (95% CI)*	n (%)
C/C	267 (60.1)	177 (39.9)	1.00	54 (12.2)	1.00	29 (6.5)
C/T	173 (62.0)	106 (38.0)	0.90 (0.66–1.23)	26 (9.3)	0.72 (0.43–1.21)	12 (4.3)
T/T	36 (54.5)	30 (45.5)	1.35 (0.79–2.33)	17 (10.6)	1.08 (0.44–2.67)	3 (4.5)
C/T + T/T	209 (60.6)	136 (39.4)	0.97 (0.72–1.30)	33 (9.6)	0.78 (0.48–1.26)	15 (4.3)
P-trend			0.70		0.52	
IL-10 -1082						
A/A	132 (59.7)	89 (40.3)	1.00	23 (10.4)	1.00	11 (5.0)
A/G	251 (61.4)	158 (38.6)	0.93 (0.66–1.31)	43 (10.5)	0.99 (0.57–1.74)	24 (5.9)
G/G	88 (59.9)	59 (40.1)	1.06 (0.68–1.63)	19 (12.9)	1.36 (0.69–2.69)	3 (4.5)
A/G + G/G	339 (61.0)	217 (39.0)	0.96 (0.70–1.34)	62 (11.2)	1.08 (0.64–1.84)	15 (4.3)
P-trend			0.87		0.42	
IL-10 Haplotype ^d						
A-C-C	85 (59.4)	58 (40.6)	1.00	19 (13.3)	1.00	8 (5.6)
G-C-C	161 (59.9)	108 (40.1)	0.93 (0.61–1.42)	30 (11.2)	0.76 (0.40–1.45)	18 (6.7)
G-T-A	197 (61.2)	125 (38.8)	0.86 (0.57–1.30)	32 (9.9)	0.66 (0.35–1.26)	15 (4.7)

* All comparisons against the no adenoma group. Multivariate OR and 95% CI models were adjusted for age tertiles (<58, 58–66, >66 yrs), sex, and race (Caucasian or not). Homozygous carriers of the more frequent gene are the reference group. The dominant model is evaluated by the OR (95% CI) for carriers of the less frequent gene combined. The co-dominant model is evaluated by P-trend

^d Composed of 3 polymorphic sites: -1082 AA/G, -819 CC/T, and -592 CC/A.

Association between the combination of change in serum cytokine concentrations from baseline and interleukin polymorphisms and colorectal adenoma recurrence among intervention group participants of the Polyp Prevention Trial (n = 808)

Table 4

Cytokine Change ^a (in pg/mL)	Interleukin Polymorphism		Adenoma Recurrence (T4)*					
	No	Any	High Risk			Advanced		
			n (%)	n (%)	OR (95% CI)*	n (%)	n (%)	OR (95% CI)*
<i>IL-1β</i>								
High > 0.01	151 (65.7)	79 (34.3)	1.00	23 (10.0)	1.00	13 (5.7)	1.00	
	93 (62.4)	56 (37.6)	1.15 (0.74–1.78)	18 (12.1)	1.40 (0.70–2.81)	9 (6.0)	1.19 (0.47–3.00)	
Low ≤ 0.01	121 (58.5)	86 (41.5)	1.34 (0.90–1.98)	17 (8.2)	0.93 (0.47–1.86)	9 (4.3)	0.81 (0.33–2.01)	
	97 (57.1)	98 (42.9)	1.41 (0.93–2.14)	25 (14.7)	1.70 (0.83–3.25)	10 (5.9)	1.28 (0.52–3.18)	
Interaction			0.78		0.60		0.68	
<i>IL-6</i>								
High > 0.04	141 (60.0)	94 (40.0)	1.00	29 (12.3)	1.00	16 (6.8)	1.00	
	77 (58.3)	55 (41.7)	1.01 (0.64–1.58)	19 (14.4)	0.98 (0.49–1.94)	11 (8.3)	0.90 (0.37–2.18)	
Low ≤ 0.04	131 (58.7)	92 (41.3)	1.04 (0.71–1.52)	25 (11.2)	0.82 (0.45–1.50)	14 (6.3)	0.83 (0.38–1.82)	
	104 (68.4)	48 (31.6)	0.70 (0.45–1.09)	11 (7.2)	0.47 (0.21–1.02)	2 (1.3)	0.14 (0.03–0.65)	
Interaction			0.20		0.30		0.06	
<i>IL-8</i>								
High > -0.01	171 (61.1)	109 (38.9)	1.00	23 (8.2)	1.00	15 (5.4)	1.00	
	68 (70.1)	29 (29.9)	0.69 (0.41–1.14)	6 (6.2)	0.74 (0.28–1.95)	3 (3.1)	0.55 (0.15–2.01)	
Low ≤ -0.01	169 (61.0)	108 (39.0)	1.00 (0.70–1.52)	37 (13.4)	1.65 (0.92–2.94)	18 (6.5)	1.19 (0.57–2.49)	
	50 (55.6)	40 (44.4)	1.17 (0.72–1.93)	10 (11.1)	1.32 (0.57–3.08)	5 (5.6)	1.02 (0.34–3.05)	
Interaction			0.13		0.90		0.61	
<i>IL-10</i>								
High > -0.04	102 (61.8)	63 (38.2)	1.00	12 (7.3)	1.00	7 (4.2)	1.00	
	134 (60.9)	86 (39.1)	1.07 (0.70–1.63)	33 (15.0)	2.23 (1.07–4.66)	20 (9.1)	2.42 (0.94–6.22)	
Low ≤ -0.04	102 (59.3)	70 (40.7)	1.12 (0.72–1.75)	21 (12.2)	1.70 (0.77–3.73)	9 (5.2)	1.29 (0.45–3.70)	
	130 (61.3)	82 (38.7)	1.08 (0.70–1.66)	18 (8.5)	1.24 (0.56–2.78)	7 (3.3)	0.87 (0.28–2.65)	
Interaction			0.72		0.03		0.07	
<i>IL-10 -8/9</i>								

Cytokine Change ^a (in pg/mL)		Interleukin Polymorphism		Adenoma Recurrence (T4) [*]							
		No		Any		High Risk				Advanced	
		n (%)	n (%)	n (%)	OR (95% CI) [*]	n (%)	OR (95% CI) [*]	n (%)	OR (95% CI) [*]	n (%)	OR (95% CI) [*]
High > -0.04	TT + TC	101 (60.8)	65 (39.2)	1.00		12 (7.23)	1.00			7 (4.2)	1.00
	CC	140 (60.9)	90 (39.1)	1.00 (0.66–1.53)		35 (15.2)	2.18 (1.05–4.51)			21 (9.1)	2.32 (0.91–5.90)
Low ≤ -0.04	TT + TC	108 (60.3)	71 (39.7)	1.01 (0.65–1.57)		21 (11.7)	1.54 (0.70–3.36)			8 (4.5)	1.01 (0.34–2.97)
	CC	127 (59.3)	87 (40.7)	1.08 (0.71–1.66)		19 (8.9)	1.25 (0.56–2.76)			8 (3.7)	0.94 (0.32–2.79)
Interaction	P-value			0.83		0.05				0.20	
High > -0.04	GG + GA	168 (61.8)	104 (38.2)	1.00		34 (12.5)	1.00			22 (8.1)	1.00
	AA	66 (58.9)	46 (41.1)	1.16 (0.74–1.84)		11 (9.8)	0.88 (0.41–1.87)			5 (4.5)	0.62 (0.22–1.75)
Low ≤ -0.04	GG + GA	171 (60.2)	113 (39.8)	1.09 (0.77–1.54)		28 (9.9)	0.79 (0.45–1.38)			10 (3.5)	0.44 (0.20–0.98)
	AA	66 (60.6)	43 (39.4)	1.05 (0.66–1.67)		12 (11.0)	0.85 (0.40–1.78)			6 (5.5)	0.63 (0.24–1.68)
Interaction	P-value			0.57		0.70				0.27	
High > -0.04	GG/GA-TT/TC-TT/TC	182 (62.1)	111 (37.9)	1.00		30 (10.2)	1.00			6 (5.5)	1.00
	AA-CC-CC	40 (56.3)	31 (43.7)	1.30 (0.76–2.22)		12 (16.9)	1.91 (0.88–4.16)			17 (5.8)	2.24 (0.88–5.71)
Low ≤ -0.04	GG/GA-TT/TC-TT/TC	176 (59.1)	122 (40.9)	1.13 (0.80–1.58)		32 (10.7)	1.02 (0.58–1.78)			8 (11.3)	0.93 (0.45–1.93)
	AA-CC-CC	45 (62.5)	27 (37.5)	1.08 (0.63–1.86)		7 (9.7)	1.07 (0.43–2.67)			0 (0.0)	
Interaction	P-value			0.43		0.33					

* Multivariate OR and 95% CI models were adjusted for age tertiles (<58, 58–66, >66 yrs), sex, average BMI (<25, 25.0–29.9, ≥30 kg/m²), race (Caucasian, non Caucasian), and current smoking status during the first 3 trial years. An increase in IL-10 concentrations was associated with a significantly greater risk of high risk adenoma recurrence in individuals homozygous with *IL-10 -592 C* and *IL-10 -819 C* compared with individuals carrying the *IL-10 -592 A* and *IL-10 -819 T* allele, respectively. The combination of decreased IL-6 concentrations and *IL-6 -174 GG* had a significantly lower risk estimate of advanced adenoma recurrence compared to the other 3 combinations. In individuals with *IL-10 -592 CC*, *IL-10 -819 CC*, and *IL-10 -1082 AA/AG*, a decrease in IL-10 concentration had a significantly lower risk estimate of advanced adenoma recurrence than an increase in IL-10 concentration. The interaction between change in IL-10 concentration and IL-10 haplotype on the risk of advanced adenoma recurrence could not be computed because no individual with a decrease in IL-10 and *IL-10 AA-CC-CC* haplotype had advanced adenoma recurrence.

^dChange in cytokine values is defined as difference between the geometric mean value of years 1 and 3 and baseline.

^bComposed of 3 polymorphic sites: *-1082 AA/G*, *-819 CC/T*, and *-592 CC/A*.

Table 5

Association between the combination of flavonol intake during the trial and interleukin polymorphisms and colorectal adenoma recurrence among intervention group participants of the Polyp Prevention Trial (n = 808)

Flavonol ^a (in mg/d)		Interleukin Polymorphism		Adenoma Recurrence (T4) [*]					
		No	Any	High Risk		Advanced			
		<i>n</i> (%)	<i>n</i> (%)	OR (95% CI) [*]	<i>n</i> (%)	OR (95% CI) [*]	<i>n</i> (%)	OR (95% CI) [*]	
<i>Mean (T1,2,3)</i>									
<i>IL-1β -511</i>									
Low ≤ 29.7	TT + CT	133 (61.0)	85 (39.0)	1.00	26 (11.9)	1.00	17 (7.8)	1.00	
	CC	98 (60.9)	63 (39.1)	0.99 (0.65–1.52)	25 (15.5)	1.44 (0.76–2.72)	13 (8.1)	1.26 (0.56–2.84)	
High > 29.7	TT + CT	139 (63.5)	80 (36.5)	0.97 (0.65–1.46)	14 (6.4)	0.59 (0.28–1.24)	5 (2.3)	0.32 (0.11–0.94)	
	CC	92 (56.3)	98 (43.7)	1.29 (0.87–1.91)	18 (11.4)	1.16 (0.58–2.34)	6 (3.8)	0.59 (0.21–1.63)	
Interaction	P-value			0.40		0.54		0.61	
<i>Mean (T1,2,3)</i>									
<i>IL-6 -174</i>									
Low ≤ 29.7	CC + CG	136 (59.1)	94 (40.9)	1.00	32 (13.9)	1.00	19 (8.3)	1.00	
	GG	91 (63.2)	53 (36.8)	0.81 (0.52–1.26)	19 (13.2)	0.80 (0.41–1.57)	11 (7.6)	0.74 (0.31–1.75)	
High > 29.7	CC + CG	136 (59.6)	92 (40.4)	1.07 (0.72–1.59)	22 (9.6)	0.80 (0.43–1.51)	11 (4.8)	0.66 (0.29–1.52)	
	GG	90 (64.3)	50 (35.7)	0.88 (0.55–1.39)	11 (7.9)	0.57 (0.26–1.25)	2 (1.4)	0.14 (0.03–0.66)	
Interaction	P-value			0.96		0.80		0.16	
<i>Mean (T1,2,3)</i>									
<i>IL-8 -251</i>									
Low ≤ 29.7	AA + AT	170 (60.1)	113 (39.9)	1.00	37 (13.1)	1.00	21 (7.4)	1.00	
	TT	58 (65.2)	31 (34.8)	0.84 (0.51–1.40)	9 (10.1)	0.76 (0.34–1.73)	7 (7.9)	1.06 (0.41–2.73)	
High > 29.7	AA + AT	170 (62.0)	104 (38.0)	1.05 (0.73–1.52)	23 (8.4)	0.80 (0.41–1.42)	12 (4.4)	0.70 (0.31–1.57)	
	TT	60 (61.2)	38 (38.8)	0.97 (0.59–1.59)	7 (7.1)	0.56 (0.23–1.38)	1 (1.0)	0.14 (0.02–1.11)	
Interaction	P-value			0.80		0.96		0.15	
<i>Mean (T1,2,3)</i>									
<i>IL-10 -592</i>									
Low ≤ 29.7	AA + AC	105 (60.7)	68 (39.3)	1.00	22 (12.7)	1.00	14 (8.1)	1.00	
	CC	129 (61.4)	81 (38.6)	1.00 (0.65–1.52)	29 (13.8)	1.04 (0.55–1.96)	17 (8.1)	1.03 (0.47–2.25)	
High > 29.7	AA + AC	99 (60.4)	65 (39.6)	1.13 (0.72–1.78)	11 (6.7)	0.59 (0.26–1.31)	2 (1.2)	0.17 (0.04–0.80)	
	CC	135 (60.8)	87 (39.2)	1.16 (0.75–1.80)	22 (9.9)	0.95 (0.47–1.89)	10 (4.5)	0.67 (0.27–1.69)	
Interaction	P-value			0.92		0.40		0.13	
<i>Mean (T1,2,3)</i>									
<i>IL-10 -819</i>									

Flavonol ^a (in mg/d)	Interleukin Polymorphism	Adenoma Recurrence (T4) [*]						
		No		Any		High Risk		Advanced
		n (%)	n (%)	OR (95% CI) [*]	n (%)	OR (95% CI) [*]	n (%)	OR (95% CI) [*]
Low ≤ 29.7	TT + TC	108 (60.7)	70 (39.3)	1.00	22 (12.4)	1.00	13 (7.3)	1.00
	CC	129 (60.3)	85 (39.7)	1.03 (0.68–1.56)	30 (14.0)	1.07 (0.57–2.00)	18 (8.4)	1.17 (0.53–2.56)
High > 29.7	TT + TC	101 (60.5)	66 (39.5)	1.10 (0.71–1.73)	11 (6.6)	0.57 (0.26–1.27)	2 (1.2)	0.18 (0.04–0.84)
	CC	138 (60.0)	92 (40.0)	1.15 (0.75–1.77)	24 (10.4)	0.99 (0.50–1.96)	11 (4.8)	0.77 (0.31–1.91)
Interaction	P-value			0.96		0.34		0.14
<i>Mean (T1,2,3)</i>								
Low ≤ 29.7	GG + GA	161 (60.1)	107 (40.9)	1.00	36 (13.4)	1.00	22 (8.2)	1.00
	AA	72 (63.2)	42 (36.8)	0.87 (0.55–1.38)	14 (12.3)	0.86 (0.43–1.73)	8 (7.0)	0.79 (0.33–1.92)
High > 29.7	GG + GA	178 (61.8)	110 (38.2)	1.03 (0.72–1.47)	26 (9.0)	0.80 (0.42–1.33)	10 (3.5)	0.46 (0.20–1.04)
	AA	60 (56.1)	47 (43.9)	1.28 (0.80–2.05)	9 (8.4)	0.57 (0.32–1.68)	3 (2.8)	0.39 (0.11–1.39)
Interaction	P-value			0.28		0.80		0.94
<i>Mean (T1,2,3)</i>								
Low ≤ 29.7	GG/GA-TT/TC-TT/TC	178 (61.6)	111 (38.4)	1.00	35 (12.1)	1.00	19 (8.3)	1.00
	AA-CC-CC	39 (55.7)	31 (44.3)	1.40 (0.82–2.40)	13 (18.6)	1.90 (0.90–4.02)	7 (7.6)	1.71 (0.66–4.42)
High > 29.7	GG/GA-TT/TC-TT/TC	180 (59.6)	122 (40.4)	1.24 (0.87–1.76)	27 (8.9)	0.89 (0.50–1.59)	11 (4.8)	0.57 (0.26–1.28)
	AA-CC-CC	46 (64.3)	27 (37.0)	1.13 (0.65–1.96)	6 (8.2)	0.83 (0.32–2.20)	2 (1.4)	0.19 (0.02–1.51)
Interaction	P-value			0.27		0.26		0.16

^{*} Multivariate OR and 95% CI models were adjusted for age tertiles (<58, 58–66, >66 yrs), sex, race (Caucasian, non Caucasian), average BMI (<25, 25.0–29.9, ≥30 kg/m²), and average energy intake (continuous) during the first 3 trial years. Individuals that consumed a flavonol-rich diet and carried *IL-6 -174 GG* had a significantly lower risk estimate of advanced adenoma recurrence compared to each of the other 3 combinations. Individuals that consumed a flavonol-rich diet and carried the *IL-1β -511 T*, *IL-10 -592 A*, or *IL-10 -819 T* allele had a significantly lower risk estimate of advanced adenoma recurrence than individuals with lower flavonol intake. In individuals with *IL-10 AA-CC-CC*, a higher flavonol intake was associated with a decreased risk of advanced adenoma recurrence compared to a lower flavonol intake. The combination of high flavonol intake and *IL-1β -511 TT/TC* had a significantly lower risk estimate of high risk adenoma recurrence than the combination of low flavonol intake and *IL-1β -511 CC*.

^a Flavonol intake below or above the median of the mean intake during the first 3 trial years (T1,2,3).

^b Composed of 3 polymorphic sites: *-1082 AA/G*, *-819 CC/T*, and *-592 CC/A*.