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Circulating levels of inflammatory cytokines and risk of colorectal adenomas

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Abstract

The association between obesity and colorectal neoplasia may be mediated by inflammation. Circulating levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are elevated in the obese. Adipose tissue can produce and release the inflammatory cytokines that are potentially procarcinogenic. We examined circulating levels of CRP, IL-6, and TNF-α in relation to risk factors and the prevalence of colorectal adenomas. Plasma levels of CRP, IL-6, and TNF-α were quantified in 873 participants (242 colorectal adenoma cases and 631 controls) in a colonoscopy-based cross-sectional study conducted between 1998 and 2002. Multivariable logistic regression was used to estimate associations between levels of inflammatory cytokines, colorectal adenomas, and known risk factors. Several known risk factors for colorectal neoplasia were associated with higher levels of inflammatory cytokines such as older age, current smoking, and increasing adiposity. The prevalence of colorectal adenomas was associated with higher concentrations of IL-6 and TNF-α, and to a lesser degree, with CRP. For IL-6, adjusted odds ratios for colorectal adenomas were 1.78 (95% confidence interval [CI]: 1.18–2.68) for the second highest plasma level, and 1.84 (95% CI: 1.24– 2.74) for the highest level compared with the reference level. A similar association was found with TNF-α, with adjusted odds ratios of 1.54 (95% CI: 1.02–2.33) and 1.65 (95% CI: 1.09–2.50), respectively. Our findings indicate that inflammation might be involved in the early development of colorectal neoplasia, and suggest that systemic inflammatory cytokines might be an indicator of obesity and other risk factors for colorectal neoplasia.

Keywords

cytokines; colorectal adenomas; obesity; inflammation

Introduction

Previous studies have shown that obesity is positively associated with colorectal adenomas and cancer [1]. Possible mechanisms for the positive association between obesity and colorectal neoplasia include the obesity-induced insulin-related pathway [1], and inflammation [2,3]. Adipose tissue is now recognized as an endocrine organ rather than a simple fat storage site, and a wide range of inflammatory cytokines are released from adipose tissue, including tumor

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necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [4,5]. Circulating levels of C-reactive protein (CRP), TNF-α, and IL-6 are elevated in the obese [6], and decrease after weight loss among the same subjects [7,8]. Based on growing evidence suggesting procarcinogenic effects of the proinflammatory cytokines [9–11], we hypothesized that systemic inflammation might mediate the association between obesity and colorectal neoplasia. The aims of the present study were (1) to examine associations of levels of CRP, IL-6 and TNF-α and colorectal cancer risk factors (older age, high BMI, and smoking) and protective factors (high physical activity and use of NSAIDs), and (2) to determine whether circulating levels of CRP, IL-6 and TNF-α were positively associated with prevalent colorectal adenomas.

Materials and Methods

Study population

Study participants were drawn from consecutive patients who underwent colonoscopy at the UNC Hospitals (Chapel Hill, NC) for a variety of indications including abdominal pain, bleeding, and, or screening between August 1, 1998 and March 4, 2000 (Diet and Health Study (DHS) III), and for screening between November 5, 2001 and December 20, 2002 (DHS IV), respectively. Patients were eligible to participate in the study if they were 30 years of age or older, could provide informed consent and complete a telephone interview, and had no known history of polyposis (>100 polyps), colon resection, colorectal cancer, colitis, or colorectal adenomas. Patients were excluded if they had inadequate preparation, or incomplete colonoscopic examinations (cecum not reached). At the time of colonoscopy all elevated lesions were biopsied or removed. Biopsy specimens were placed in formalin and submitted directly to pathology for sectioning and staining. A single experienced study pathologist (J.T.W) examined all pathologic specimens and used a standardized form to record the total number of polyps and the maximum diameter (in millimeters), location, histologic type and atypia grade of each polyp. Any polyp with tubular, tubulovillous or villous pathology, or that had mixed adenomatous and hyperplastic characteristics, was classified as an adenoma.

Data collection

DHS research staff weighed all subjects and measured their height, waist and hip circumferences prior to colonoscopy. Information about demographic characteristics, education, medical history, NSAID use, smoking and other lifestyle exposures was collected by telephone interview within 12 weeks of the colonoscopy using a structured questionnaire. Dietary intake was assessed using the Block food frequency questionnaire (DHS III) [12] and the NCI quantitative food frequency questionnaire (DHS IV) [13]. Physical activity was estimated by computing weekly energy expenditure in METs (Metabolic Equivalents – a standard measure of activity) based on the duration and intensity of various occupational and non-occupational activities during typical days in the previous year. This study was approved by the institutional review board at the University of North Carolina School of Medicine.

Samples for analyses

There were 2,162 patients (926 for the DHS III and 1,236 for the DHS IV) who met the eligibility criteria described above. Overall, 84.3% of the eligible patients (N = 1,822) were asked to participate in the study; of these, 89.6% (N = 1,633) agreed. Telephone interviews were completed with 75.5% of the subjects who consented to participate (N = 1,233). The final study sample consisted of 873 participants (327 for the DHS III and 546 for the DHS IV) with plasma samples for cytokine assays. There were slightly more men in the final study sample (45% vs. 40%, $p < 0.04$), compared with those who were interviewed but not included in cytokine assays. However, there were no significant differences in other demographic characteristics such as age and race.

Laboratory methods

Specimen collection and handling conditions were similar for DHS III and IV. Fasting blood samples were collected from participants at the time of colonoscopy. Plasma was extracted from blood samples and stored in aliquots at −80°C until analyses. Plasma concentrations of inflammatory cytokines were quantified using commercially available ultrasensitive ELISA kits for human CRP (Biosource, Carlsbad, CA), and human IL-6 and TNF-α (Diagnostic System Laboratories Inc., Webster, TX). Minimum detection levels were 1.6 ng/ml for CRP, 0.104 pg/ml for IL-6, and 0.09 pg/ml for TNF-α, according to the manufacturers. All assays were run in duplicate, and levels were classified according to the average of each pair of measurements. The intra- and inter-assay coefficients of variation were 2.8% and 0.19% for CRP at 100 ng/ml; 11.3% and 16.9% for IL-6 at 0.16 pg/ml; and 5% and 11.2% for TNF-α at 1 pg/ml, respectively.

Statistical analysis

Selected characteristics were compared between cases and controls, and chi-square tests were used to assess differences in proportions. Median and interquartile ranges for each inflammatory cytokine were calculated according to case/control status. Mann-Whitney U test p-values were calculated to evaluate the difference in circulating levels of each inflammatory cytokine by case/control status because levels of inflammatory cytokines were not normally distributed on raw or log-transformed scales. Spearman's rank test was used for correlations between circulating levels of three inflammatory cytokines.

Logistic regression was used to evaluate associations between risk factors for colorectal neoplasia and high levels of inflammatory cytokines (CRP, IL-6 and TNF-α, dichotomized as described below), after adjustment for age (30–49, 50–64, ≥65 years) and sex. Subjects were classified as having high CRP or TNF-α if their measured levels were greater than or equal to the value of the 66^{th} percentile in the distribution of each cytokine among controls. For IL-6, 630 subjects (50% of cases and 65% of controls) had values below the detection limit; therefore, we classified subjects as having high IL-6 if their levels were greater than or equal to the median value among controls with detectable values (0.3571 pg/ml).

Risk factors for colorectal neoplasia that were evaluated for associations with inflammatory cytokines were age at colonoscopy (30–49, 50–64, ≥65 years), sex, regular use of NSAIDs (use ≥ 3 times per week during the past 5 years), smoking status (current, former, or never), physical activity (average levels in the prior year categorized into tertiles based on the distribution among controls), average daily total energy and fat intakes in the prior year (tertiles based on distribution among controls), and obesity (measured by body mass index [BMI] alone or BMI combined with waist circumference). BMI was categorized based on the World Health organization (WHO) definitions [14] as obese (BMI ≥ 30 kg/m^2), overweight (BMI 25–29 kg/m^2), and normal weight or underweight (BMI < 25 kg/m^2). Waist circumference was categorized according to the American Diabetes Association criteria for abdominal obesity as action level 1 (men ≥ 94 cm, women ≥ 80 cm), action level 2 (men ≥102 cm, women, ≥ 88 cm) or normal [15].

Odds ratios (ORs) and 95% confidence intervals for associations between colorectal adenomas and each inflammatory cytokine were estimated using unconditional logistic regression models. CRP and TNF-α were categorized based on tertile distributions among controls, with the lowest tertile serving as the referent exposure category for each cytokine. For IL-6, subjects with values below the detection limit in the assay were the referent exposure category, and the remaining subjects were categorized into two groups using the median IL-6 level among controls with detectable values (0.3571 pg/ml) as a cut point.

Based on a directed acyclic graph (DAG) [16], age (30–49, 50–54, 55–59, 60–65, 65–69, 70–74, ≥75 years), sex, smoking status, regular use of NSAIDs, comorbidity (defined as presence of arthritis, diabetes, hypertension, or heart attack), study phase (DHS 3, or DHS 4), daily total energy and fat intakes, physical activity and BMI were considered as potential confounding factors. To determine which covariates should be entered in the final multivariate models, we constructed a full model with all potential confounders, and assessed change in beta coefficients for high levels of inflammatory cytokines versus the reference categories in relation to occurrence of colorectal adenomas. Age and sex were included in all models, and other covariates were retained if the beta coefficient for any cytokine changed by more than 10% when they were removed. Final models for each inflammatory cytokine included age (30–49, 50–64, or ≥65), sex and obesity (assessed by BMI combined with waist circumference: BMI <25; BMI 25–29.9 kg/m^2 and action level 1 abdominal adiposity; BMI 25–29.9 kg/m^2 and action level 2 abdominal adiposity; BMI ≥ 30 kg/m^2 and action level 1 abdominal adiposity; or BMI ≥ 30 kg/m^2 and action level 2 abdominal adiposity).

Levels of each inflammatory cytokine were compared between case subgroups defined according to villous histology (villous or non-villous), the size of the largest adenoma (<10 mm or ≥ 10 mm in diameter), and the presence of multiple adenomas (1, or ≥ 2 adenomas). Participants with more than one adenoma were classified based on the most advanced or largest adenoma, respectively. Mann-Whitney U tests were used to assess median differences in cytokine levels between case subtypes.

All statistical tests were two-sided. All analyses were performed using Stata version 9.0 (Texas Station, TX).

Results

Selected characteristics of colorectal adenoma cases and controls are shown in Table 1. The median age was 58 years in cases and 54 years in controls. Compared with controls, cases were more likely to be male, and were less likely to have used NSAIDs regularly in the past 5 years. Cases were also more likely to self-report comorbid conditions (arthritis, hypertension, heart attack or diabetes.) Although associations did not reach statistical significance, cases were also more likely to be current smokers, obese (based on both BMI and waist circumference), and less physically active, and to have had higher total energy and fat intakes than controls.

The median level of TNF-α was 1.962 pg/ml (IQR: 1.419–2.277) in cases and 1.843 pg/ml (IQR: 1.199–2.470) in controls (Mann-Whitney U test, $p < 0.0034$). For CRP, the median concentration was 7,582.4 ng/ml (interquartile range: 2,376.9 – 16,823.3) in cases and 5,699.04 ng/ml (interquartile range: 2,066.3 – 15,646.4) in controls. The median difference in CRP levels was not statistically significant ($p = 0.2547$). Median IL-6 levels were zero in both cases and controls; however, the Mann-Whitney U test p-value was highly significant ($p < 0.001$), indicating that the IL-6 concentration of a randomly selected case was higher than would be expected by chance alone, compared with the IL-6 concentration of a randomly selected control. The three cytokines were significantly, but only weakly correlated with one another; the Spearman's (Rho) correlation coefficients were 0.3431 between CRP and IL-6, 0.3239 between IL-6 and TNF-α, and 0.2028 between CRP and TNF-α (all p-values < 0.001).

Many known risk factors for colorectal neoplasia were positively associated with high levels of CRP, IL-6 and TNF-α (Table 2). Older age, current smoking, and higher adiposity were positively associated with prevalence of high levels of the inflammatory cytokines. When considered in combination with action level 2 abdominal adiposity, BMI ≥ 30 (kg/m^2) appeared to be more strongly related to high levels of inflammatory cytokines than when considered alone, particularly for CRP (OR = 5.36, 95% CI: 3.61–7.96 for BMI ≥ 30 [kg/m^2], and OR =

6.26, 95% CI: 4.04–9.68 for BMI ≥ 30 [kg/m^2] and action level 2 abdominal adiposity). This association did not vary between men and women (*p* for interaction between obesity and sex in relation to high levels of CRP = 0.8115).

Subjects in the highest tertiles of total energy and fat intakes were more likely to have high CRP than those in the lowest tertiles of intakes. Subjects in the highest tertile of fat intake were also more likely to have high IL-6 and TNF-α than those in the lowest tertile of fat intake. Prevalence of high CRP and TNF-α was inversely associated with physical activity above the reference level. Although regular use of NSAIDs is a generally-accepted protective factor for colorectal neoplasia, regular users of NSAIDs in this study had a slightly increased prevalence of high levels of inflammatory cytokines relative to non-regular users. Finally, women were more likely to have high CRP than men, although there was no association between sex and IL-6 or TNF-α.

Table 3 shows crude and adjusted odds ratios and 95% confidence intervals for associations between colorectal adenomas and plasma levels of inflammatory cytokines. Overall, the prevalence of colorectal adenomas was positively associated with IL-6 and TNF-α above reference levels. Specifically, for IL-6, adjusted odds ratios for colorectal adenomas were 1.78 (95% CI: 1.18–2.68) for the second highest category, and 1.84 (95% CI: 1.24–2.74) for the highest category compared with the reference category. A similar association was found with TNF-α, for which adjusted odds ratios for the second and third highest levels were 1.54 (95% CI: 1.02–2.33) and 1.65 (95% CI: 1.09–2.50), respectively. The prevalence of colorectal adenomas was also slightly increased in association with the highest category of circulating CRP only (adjusted OR = 1.45, 95% CI: 0.95–2.23).

To evaluate whether higher levels of circulating inflammatory cytokines were associated with advanced pathological features of colorectal adenomas, we performed separate analyses comparing adenoma subtypes. Out of 242 adenoma cases, 22 (9%) had adenomas with villous histology, 56 (23%) had adenomas ≥10 mm in diameter, and 48 (20%) had more than 1 adenoma. The median CRP level was 11,480.34 ng/ml (IQR: 5,760.25, 25,263.24) for adenoma with villous histology, and 7,050.6 ng/ml (IQR: 2,302.28, 16,504.8) for adenomas with no villous component (Mann-Whitney U test, $p < 0.0391$). There was no significant difference in median concentrations of IL-6 and TNF-α according to villous histology. In addition, levels of inflammatory cytokines were not associated with large adenomas or multiple adenomas.

Discussion

In this colonoscopy-based cross-sectional study of colorectal adenomas, circulating levels of IL-6 and TNF-α, and to a lesser degree CRP, were positively associated with the prevalence of colorectal adenomas. Several known risk factors for colorectal neoplasia also were associated with high levels of inflammatory cytokines, specifically older age, current smoking, increasing adiposity, physical inactivity, and higher caloric and fat intake.

Previous studies have not evaluated associations between cytokine levels and colorectal adenomas, but several have evaluated associations with colorectal cancer, with mixed results. Our findings for adenomas are in agreement with results for colorectal cancer from a nested case-control study in the CLUEII cohort, in which Erlinger *et al.*[18] found a positive association with the highest quartile of CRP at baseline compared to the lowest quartile. Two prospective studies based on a Japanese population [19] and a cohort of Finish male smokers [20] also support an association between CRP and colorectal cancer, but there was no clear relationship between CRP and colorectal cancer in the Women's Health Study [21], or in the Japan Collaborative Cohort Study [22]. Few studies have evaluated plasma levels of IL-6 or TNF-α in relation to colorectal neoplasia. Among older adults (aged 70–79 years) participating in the Health Aging

and Body Composition study, IL-6 and TNF-α as well as CRP were positively associated with incident cancers and cancer deaths [23]. However, cancer site-specific estimates of associations with each cytokine were not presented.

Accumulating evidence suggests that systemic inflammation might be a plausible mechanism for colon carcinogenesis. Studies have shown that genetic variations in inflammation-related genes such as IL-6, IL-8 and IL-10 are associated with susceptibility to colorectal cancer and adenomas [3,9]. IL-6 appears to stimulate cell growth, and inhibit apoptosis [2,11]. TNF-α is a key cytokine that is involved in the regulation of cytokines during inflammatory responses [10]. Although TNF-α was first identified as a host-induced substance that is selectively toxic to tumor cells at high doses [24], at physiologic levels TNF-α promotes cellular proliferation and inhibits apoptosis, at least partly by inducing NF-κB [10]. CRP upregulates the expression of adhesion molecules, and increases the release of IL-1, IL-6, IL-18, and TNF-α from mononuclear phagocytes [25].

With regard to associations between inflammatory cytokines and risk factors for colorectal neoplasia, our findings are largely in agreement with previous studies. Obesity is a known risk factor for colorectal neoplasia, and has recently been characterized as a state of low-grade systemic inflammation [6]. Circulating levels of inflammatory cytokines were elevated in obese individuals compared with lean persons [26], and levels have been shown to decrease after weight loss [7,27]. It is now recognized that adipose tissue can synthesize and release cytokines such as TNF-α and IL-6 [28]. Strong positive associations between obesity and levels of the proinflammatory cytokines in our study were consistent with expectations given that adipose tissue is a source of cytokines. CRP and IL-6 levels increase with chronological age [29,30], but it remains unclear whether this occurs as a consequence of aging or is simply a reflection of underlying health conditions that are more common with increasing age [31]. Smoking also has been associated with elevated levels of CRP and IL-6 [32–34]. Although the effect of smoking on inflammatory cytokines appeared to persist for several years after smoking cessation in one study [33], only current (not past) smoking was associated with high levels of inflammatory cytokines in our study. In addition, high levels of physical activity have been associated with decreased concentrations of CRP, IL-6 and TNF-α, independent of obesity [35].

Weak positive associations between regular use of NSAIDs and high levels of inflammatory cytokines were contrary to our expectations. This could have been due to confounding by indication because comorbidity was related both to regular use of NSAIDs and to high levels of inflammatory cytokines. However, adjustment for comorbidity did not change the direction of associations, although the strength of the associations was slightly attenuated. Alternatively, inflammatory cytokines measured at the time of colonoscopy may not have reflected typical levels among regular NSAID users, since it is recommended that patients abstain from NSAID use for one week prior to colonoscopy. A positive association between NSAIDs and cytokines might be evident if cytokine levels among regular users are elevated relative to non-users in the absence of NSAID use. Finally, the protective effect of NSAIDs might not be exerted via modifying circulating cytokines, as we hypothesized. There have been inconsistent findings; while aspirin administration has been shown to reduce levels of CRP by 29% and IL-6 by 37% in angina patients [36], Feldman *et al.* did not detect any significant change in serum CRP levels with low dose aspirin use [37].

Our study has several strengths. First, colorectal adenomas were completely ascertained by colonoscopy to the cecum, and were reviewed by a single experienced pathologist. Also, detailed information on exposure history enabled the assessment of a wide range of potential confounding factors as well as the evaluation of relations between inflammatory cytokines and risk factors for colorectal neoplasia.

The temporal ambiguity inherent in a cross-sectional study is a limitation, but it is unlikely that adenomas themselves would cause a systemic increase in inflammatory cytokines. In our study, the median size of the largest adenoma was only 5 millimeters, and macrophage infiltration, which is uncommon in adenomas in general, is particularly rare in small adenomas [38]. We recognize that a one time measurement of circulating inflammatory cytokines may not represent an individual's inflammatory status during the development of adenomas, and that measured levels may be influenced by diurnal or stress induced variation. For example, patients in our study could have experienced a short-term increase in plasma levels of CRP, IL-6 and TNF-α given that they were awaiting colonoscopy, which may be a stressful event. However, stress-induced activation of cytokines [39] would have not differed by case/control status. In addition, while there is a report that TNF-α is significantly lower in the morning than in the evening [40], CRP [41] and IL-6 [40] are tightly regulated over time, and are not affected by circadian variation [40]. Lastly, our finding that IL-6 levels were below the detection limit in about 50% of cases and 65% of controls was consistent with expectations, since it has been recognized that IL-6 is generally undetectable in healthy individuals without infection, trauma or other inflammatory conditions [42].

We have shown associations between the prevalence of colorectal adenomas and increased levels of IL-6 and TNF-α, and, to a lesser degree, CRP. These findings indicate that inflammation might be involved in the early development of colorectal neoplasia, and suggest that systemic inflammatory cytokines might be an indicator of obesity and other risk factors.

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Abbreviations used in this paper

BMI, Body mass index
CI, Confidence interval
CRP, C-reactive protein
ELISA, Enzyme-linked immunosorbent assay
HL, Hodges-Lehmann estimator
IL-6, Interleukin-6
IQR, Interquartile range
NSAID, Non-steroidal anti-inflammatory drug
OR, Odds ratio
TNF-α, Tumor necrosis factor-α
WHO, World Health Organization

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Table 1

Selected characteristics of colorectal adenoma cases and controls, Diet and Health Study, 1998–2002

Characteristics	Cases (N = 242)		Controls (N = 631)		p-value*
	No.	%	No.	%	
Age (years)					
30–49	45	18.6	173	27.5	
50–64	125	51.7	335	53.2	
≥ 65	72	29.8	122	19.4	0.001
Median age	58		54		
Sex					
Male	144	59.5	250	39.6	
Female	98	40.5	381	60.4	<0.001
Regular use of NSAIDs					
Yes	100	45.3	323	55.3	
No	121	54.8	261	44.7	0.011
Smoking status					
Never	95	43.4	299	51.2	
Past smokers	88	40.2	208	35.6	
Current smokers	36	16.4	77	13.2	0.13
Body mass index (kg/m^2)					
< 25	80	33.6	248	40.6	
25 – 29.9	90	37.8	213	34.9	
≥ 30	68	28.6	150	24.6	0.131
Median body mass index	26.84		26.15		
Abdominal obesity†					
Normal	34	19.2	131	25.8	
Level 1	47	26.6	116	22.9	
Level 2	96	54.2	260	51.3	0.187
Comorbidity‡					
Yes	144	65.2	336	57.6	
No	77	34.8	247	42.4	0.052
Physical activity (average MET-minutes/day)					
1st tertile (<2400)	76	39.8	175	32.5	

Characteristics	Cases (N = 242)		Controls (N = 631)		p-value*
	No.	%	No.	%	
2nd tertile (2400 – 15269)	65	34.0	183	34.0	
3rd tertile (≥ 15270)	50	26.2	180	33.5	0.104
Median physical activity	2670		2973		
Total energy intake (kcal/day)					
1st tertile (1389.11)	61	29.5	183	33.3	
2nd tertile (1389.11 – 1935.63)	64	30.9	183	33.3	
3rd tertile (≥ 1935.64)	82	39.6	184	33.5	0.279
Median energy intake	1757.72		1598.18		
Total fat intake (g/day)					
3rd tertile (47.05)	64	30.9	183	33.3	
2nd tertile (47.05 – 72.88)	60	29.0	183	33.3	
3rd tertile (≥ 72.89)	83	40.1	184	33.5	0.223
Median fat intake	63.85		59.57		

† Defined based on waist circumference. In women, <80 (cm) defined as normal, 80–87.9 as action level 1, and ≥ 88 as action level 2 abdominal obesity. In men, <94 defined as normal, 94–101.9 as action level 1, and ≥102 as action level 2 abdominal obesity.

≠ Defined as presence of arthritis, diabetes, hypertension, or heart attack

* P-values are based on chi-square statistics

Table 2

Multivariable† associations of risk factors for colorectal neoplasia and high levels of inflammatory cytokines, Diet and Health Study, 1998–2002

Risk factors	OR (95% CI)		
	CRP (≥12013.1ng/ml)	IL-6 (≥0.3571pg/ml)	TNF-α (≥2.2358pg/ml)
Age (years)			
50–64	1.39 (0.97–2.0)	1.6 (1.02–2.5)	1.16 (0.82–1.65)
≥ 65	1.62 (1.06–2.48)	2.17 (1.31–3.59)	1.94 (1.29–2.91)
Female sex	2.25 (1.67–3.04)	0.85 (0.61–1.19)	0.94 (0.71–1.25)
Regular use of NSAIDs	1.19 (0.88–1.62)	1.47 (1.03–2.12)	1.34 (1.0–1.81)
Smoking status			
Current	2.05 (1.31–3.23)	2.59 (1.6–4.2)	1.23 (0.79–1.91)
Past	0.85 (0.61–1.2)	1.01 (0.67–1.51)	0.93 (0.67–1.29)
Obesity			
BMI 25 – 29.9 (kg/m^2)	1.94 (1.34–2.83)	1.85 (1.22–2.83)	1.46 (1.04–2.05)
Level 1 abdominal adiposity‡	1.75 (1.1–2.79)	1.93 (1.17–3.18)	1.44 (0.95–2.2)
Level 2 abdominal adiposity‡	2.1 (1.33–3.23)	1.71 (0.83–3.55)	1.46 (0.96–2.22)
BMI ≥ 30 (kg/m^2)	5.36 (3.61–7.96)	2.47 (1.58–3.85)	1.91 (1.32–2.76)
Level 1 abdominal adiposity‡	3.54 (1.9–6.6)	1.74 (1.04–2.92)	1.63 (0.89–2.97)
Level 2 abdominal adiposity‡	6.26 (4.04–9.68)	2.81 (1.73–4.56)	2.03 (1.35–3.05)
Physical activity (MET-minutes/day)			
2nd tertile*	0.74 (0.5–1.09)	0.71 (0.44–1.14)	0.69 (0.47–1.01)
3rd tertile*	0.65 (0.43–0.99)	1.09 (0.68–1.74)	0.73 (0.49–1.09)
Daily energy intake (kcal)			
2nd tertile*	1.06 (0.72–1.56)	0.73 (0.45–1.17)	0.80 (0.55–1.16)
3rd tertile*	1.45 (0.97–2.16)	1.16 (0.74–1.81)	1.02 (0.7–1.49)
Total daily fat intake (g)			
2nd tertile*	1.01 (0.68–1.5)	0.92 (0.57–1.48)	0.86 (0.58–1.25)
3rd tertile*	1.48 (1.0–2.19)	1.29 (0.82–2.04)	1.24 (0.85–1.81)

† Adjusted for age (30–49, 50–64, ≥65 years) and sex

‡ Defined based on waist circumference. In women, <80 (cm) defined as normal, 80–87.9 as action level 1, and ≥ 88 as action level 2 abdominal obesity. In men, <94 defined as normal, 94–101.9 as action level 1, and ≥102 as action level 2 abdominal obesity.

* Tertiles are based on the distribution among controls.

Table 3

Crude and adjusted† odds ratios (OR) and 95% confidence intervals (CI) for associations between colorectal adenomas and plasma levels of inflammatory cytokines, Diet and Health Study, 1998–2002

	Cases		Controls		OR (95% CI)	Adj. † OR (95% CI)
	No.	%	No.	%		
CRP						
<2916.03	71	30.34	204	33.28	1.	1.
2916.03–12013	75	32.05	204	33.28	1.06 (0.72–1.54)	0.99 (0.66–1.50)
≥12013.1	88	37.61	205	33.44	1.23 (0.85–1.78)	1.45 (0.95–2.23)
IL-6						
0	122	50.83	403	64.86	1.	1.
<0.3571	54	22.5	110	17.49	1.64 (1.12–2.41)	1.78 (1.18–2.68)
≥0.3571	64	26.67	111	17.65	1.93 (1.33–2.79)	1.84 (1.24–2.74)
TNF-α						
<1.3877	53	22.36	209	33.28	1.	1.
1.3877–2.2357	89	37.55	209	33.28	1.68 (1.14–2.48)	1.54 (1.02–2.33)
≥2.2358	95	40.08	210	33.44	1.78 (1.21–2.63)	1.65 (1.09–2.50)

† Adjusted for age (30–49, 50–54, 55–59, 60–65, 65–69, 70–74, ≥75 years), sex and obesity (BMI<25 kg/m^2; BMI 25–29.9 kg/m^2 and action level 1 abdominal adiposity; BMI 25–29.9 kg/m^2 and action level 2 abdominal adiposity; BMI ≥30 kg/m^2 and action level 1 abdominal adiposity; or BMI ≥30 kg/m^2 and action level 2 abdominal adiposity)