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Plasma inflammatory markers and risk of advanced colorectal adenoma in women

Mingyang Song[1,2,3,4], **Raaj S. Mehta**[1,2], **Kana Wu**[3], **Charles S. Fuchs**[5,6], **Shuji Ogino**[4,6,7], **Edward L. Giovannucci**[3,4,5], and **Andrew T. Chan**[1,2,5]

[1]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, United States

[2]Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts, United States

[3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

[5]Channing Division of Network Medicine, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States

[6]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States

[7]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States

Abstract

Evidence remains inconclusive about the association of systemic inflammatory markers with colorectal neoplasia. We investigated whether circulating inflammatory markers were associated with risk of advanced colorectal adenoma. We measured plasma macrophage inhibitory cytokine-1 (MIC-1), C-reactive protein (CRP), interleukin-6 (IL-6), and soluble tumor necrosis factor receptor 2 (sTNFR-2) in blood samples drawn from 32,826 women in 1989-1990 in the Nurses' Health Study. Through 2008, we documented 757 cases of advanced colorectal adenomas (≥1cm or any size with advanced histology); each case was matched by age and time of blood draw with one control randomly selected from participants who underwent lower endoscopy and did not have neoplasia. Plasma MIC-1 was associated with higher risk of advanced adenoma (P_{trend}=0.04), with an odds ratio of 1.55 (95% CI, 1.03-2.32) comparing extreme quintiles of MIC-1 after adjusting for colorectal cancer-risk factors and other inflammatory markers. Among cases, MIC-1 level was positively associated with the number of adenomas (P<0.001) and gradually increased from adenomas located in the rectum, distal colon, and up to the proximal

Corresponding author: Andrew T. Chan, Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, 55 Fruit St, Boston, Massachusetts 02114, United States., Telephone: +01- 617-726-3212, Fax: +01- 617-724-6832, achan@partners.org.

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colon. There was a strong positive association between MIC-1 and risk of adenomas with multiplicity, ≥1cm size and location in the proximal colon (all P_{trend}<0.05). CRP, IL-6 or sTNFR-2 was not associated with adenoma risk. In conclusion, plasma MIC-1 was associated with higher risk of colorectal adenoma, especially multiple, large and proximal adenomas. Our results provide further support for a role for MIC-1 in carcinogenesis and the potential for MIC-1 as an adjunctive biomarker for detection of advanced colorectal adenoma.

Keywords

growth differentiation factor 15; systemic inflammation; pathology; colonoscopy

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the world.(1) Inflammation has been implicated in the initiation and progression of CRC.(2) Patients with ulcerative colitis and Crohn's colitis demonstrate chronic inflammation in the gastrointestinal mucosa and are at increased risk of developing CRC.(3) Conversely, regular use of anti-inflammatory medications such as aspirin has been associated with lower risk of CRC(4) as well as colorectal adenomas, (5-8) precursors of most CRC.

Despite the preponderance of evidence implicating chronic inflammation in colorectal carcinogenesis, epidemiologic data remain inconclusive about the association between systemic inflammatory markers and colorectal neoplasia. Circulating C-reactive protein (CRP), a liver-derived acute phase protein that is elevated in chronic inflammatory conditions, has been associated with an increased risk of CRC in 7(9-15) of the 18 prospective studies that have been published to date.(9-25) Studies examining the association of other inflammatory cytokines, such as interleukin-6 (IL-6) (10, 22-24, 26) and tumor necrosis factor (TNF)-α,(23, 26, 27) with CRC are limited and inconsistent. Recently, macrophage inhibitory cytokine-1 (MIC-1, also known as growth differentiation factor 15, GDF15), a divergent member of the human transforming growth factor (TGF)-β superfamily and a mediator of the systemic inflammatory response,(28) has been related to development of cancers in various organs,(29-32) including CRC.(33) We recently showed that elevated levels of plasma MIC-1 were associated with higher risk of incident CRC.(34)

However, there are limited data about the association of inflammatory markers with colorectal adenomas. The 5 studies that have prospectively assessed the relationship between circulating CRP and colorectal adenomas have each reported null associations (35-38) except one study which observed an inverse association between serum CRP and risk of adenomas.(39) In the Polyp Prevention Study, serum MIC-1 was associated with the presence of colorectal adenomas and their recurrence 3 years later. However, this analysis was limited by the large variation in the time of MIC-1 measurement with respect to colonoscopy, which compromises its ability to determine whether MIC-1 elevation was a predisposing factor or consequence of colorectal adenoma.(40) For IL-6 and TNF-α, the only available study did not find any association with risk of recurrent adenomas.(38)

Given the sparse data, we prospectively examined measures of plasma MIC-1, CRP, IL-6, and soluble tumor necrosis factor receptor 2 (sTNFR-2, also known as TNF receptor superfamily member 1B, TNFRSF1B), a surrogate marker for TNF-α, with the incidence of advanced colorectal adenomas in a case-control study nested within the Nurses' Health Study (NHS).

Materials and Methods

Study population

The NHS included 121,701 U.S. registered female nurses who were aged 30-55 years in 1976. Detailed description of the cohort has been provided elsewhere.(41) Briefly, follow-up questionnaires were administered biennially to collect and update medical, lifestyle, and other health-related information; validated food frequency questionnaires (FFQs) were completed in 1980, 1984, 1986 and every 4 years thereafter to update dietary information. The follow-up rate had been 95.6% among participants who were alive up to 2008. Between 1989 and 1990, 32,826 women returned a blood specimen on ice packs by overnight courier. The procedures for blood collection, handling and storage, have been previously summarized.(42) Written informed consent was obtained from all participants, and the study protocol was approved by the Institutional Review Board at the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Selection of colorectal adenoma cases and control subjects

Women were eligible for selection as either an adenoma case subject or a control subject if they had provided a blood specimen in 1989-1990 and reported having at least one sigmoidoscopy or colonoscopy from 1990 through 2008 after blood donation. Women who had a history of inflammatory bowel disease, a familial polyposis syndrome, or diagnosed adenoma or cancer (except non-melanoma skin cancer) prior to blood draw were excluded. When a participant reported a polyp on a biennial questionnaire, we asked for her permission to obtain medical records and pathology reports. With each biennial questionnaire, we obtained records on over 90% of reported polyps. Study investigators, blinded to risk factors and other medical history, reviewed all records and extracted data on histologic type, anatomic location, and size of polyps. We classified adenoma cases into proximal colon (from cecum to splenic flexure), distal colon (descending colon and sigmoid) and rectal adenomas (rectosigmoid and rectum).

For the current study, we included cases of advanced adenomas, defined as adenomas of at least 1 cm in diameter or any size with tubulovillous, villous, or high-grade dysplasia, as previously described.(7) Using risk set sampling, we randomly selected one control subject (i.e., women who did not report a polyp, including hyperplastic, on endoscopy) for each case matched on date of endoscopy (i.e., during the same 2-year period), birth year, indication for endoscopy, time period of endoscopy prior to adenoma diagnosis, month and year of blood draw, and fasting status. A total of 1514 women (757 case subjects and 757 control subjects) were included in this analysis.

Laboratory assays

All laboratory assays for plasma inflammatory markers were performed at the laboratory of Dr. Nader Rifai at Boston Children's Hospital (Massachusetts, USA). We used enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, USA) to measure levels of MIC-1 (GDF15), IL-6 and sTNFR-2, and a highly sensitive immunoturbidimetric assay (Denka Seiken Co, Tokyo, Japan) to measure CRP levels in the archived prediagnostic plasma specimens. Samples from cases and their matched controls were analyzed in the same batch. Quality control samples were randomly interspersed among the case-control samples. Personnel blinded to quality control and case-control status conducted all assays.

The biomarkers were assayed in two batches over 6 years apart and drift samples were included to assess laboratory drift over time. The intraclass correlation between measurements of the two drift batches was 0.99 for MIC-1, 0.97 for CRP, 0.97 for IL-6, and 0.82 for sTNFR-2. To minimize the batch effect, we corrected biomarker concentrations for measurement batch using the average batch correction method,[43] with adjustment for age, body mass index (BMI) and case control status. The mean intra-assay coefficient of variation from blinded quality control samples was 4.8% for MIC-1, 5.5% for CRP, 12.7% for IL-6, and 15.9% for sTNFR-2.

Statistical analysis

We categorized plasma markers into quantiles on the basis of their distributions among control participants. Conditional logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) of advanced adenomas in relation to biomarkers. Test for trend was performed using the median value for each quintile as a continuous variable in the regression models. We assessed the potential nonlinear relationship between biomarkers and adenoma risk using stepwise restricted cubic spline analysis,(44) with a $P = 0.05$ as the criteria for both inclusion and retention in the model. In the multivariable analyses, we adjusted for several risk factors for colorectal neoplasia. Details regarding the assessment of covariates are provided in the Supplementary Materials.

We compared the median levels of biomarkers among adenoma cases diagnosed with distinct pathologic characteristics using the Kruskal-Wallis test. To examine the independent associations between adenoma characteristics and biomarker concentrations, we performed a multivariable linear regression of log-transformed measurements of biomarkers on adenoma features.

We then examined the association between biomarker levels and adenoma risk according to pathologic features of adenoma. We also performed stratified analyses to evaluate whether the observed associations vary by lifestyle factors.

We used SAS version 9.3 (SAS Institute, Inc, Cary, NC) for all analyses. All statistical tests were two-sided and $P< 0.05$ was considered statistically significant.

Results

As shown in Table 1, women diagnosed with advanced adenoma were heavier and more likely to smoke at baseline than controls. In contrast, control subjects consumed more calcium and had higher AHEI scores than cases. Plasma MIC-1, CRP and sTNFR-2 levels were higher among cases than controls (P=0.04, 0.01 and 0.07, respectively). On average, cases were diagnosed about 10 years after blood collection. Most cases had adenomas in the colon, especially in the distal colon (41%), while only 13% cases had adenomas in the rectum.

Plasma concentrations of MIC-1, CRP, IL-6 and sTNFR-2 were positively correlated, with a Spearman correlation coefficient ranging from 0.19 to 0.41 (Table 2). Compared to CRP, IL-6 and sTNFR-2, MIC-1 demonstrated a distinct pattern of association with age and lifestyle factors: MIC-1 levels were modestly associated with age (r=0.48) and weakly with pack-years of smoking (r=0.13), but not with BMI (r=0.04), physical activity(r=0.02), alcohol consumption (r=-0.06) or dietary score AHEI (r=0.05). In contrast, CRP, IL-6 and sTNFR-2 were less age-dependent, and generally showed a weaker correlation with smoking, but a stronger correlation with BMI, alcohol consumption and dietary AHEI score.

Elevated levels of plasma MIC-1 were associated with higher risk of advanced colorectal adenoma (Table 3). Compared to women in the lowest quintile, the OR of advanced adenoma among those at the highest quintile of MIC-1 was 1.55 (95% CI, 1.03-2.32, P_{trend}=0.04), after adjusting for several potential confounders and other inflammatory markers. In spline analysis, no spline variable was selected into the model, indicating that the association did not deviate from linearity. Excluding cases diagnosed within the first 4 years after blood draw did not materially change the association (OR=1.43;95% CI, 0.94-2.18). Similar results were also obtained after restricting the cohort to individuals who had at least one negative endoscopy prior to blood draw (OR=1.47;95% CI, 0.86-2.53). In addition, we stratified by the time period of the prior endoscopy before adenoma diagnosis, which was one of matching factors. The results did not differ between those who had a negative endoscopy within 4 years prior to adenoma diagnosis and those who did not (data not shown).

In contrast, plasma CRP,IL-6 or sTNFR-2 was not associated with adenoma risk after adjusting for potential confounders and other inflammatory markers, with a OR of 1.10 (95% CI, 0.76-1.59), 0.96 (95% CI, 0.65-1.42), and 0.89 (95% CI, 0.60-1.33) comparing the highest to the lowest quintiles, respectively (Table 3).

We then compared the median biomarker concentrations between certain case subgroups defined by adenoma characteristics. As shown in Table 4, MIC-1 levels were higher among cases with multiple (≥2) adenomas than those with single adenomas (P<0.001). Cases with large adenomas, defined by ≥1cm diameter, also had higher MIC-1 levels than those with small adenomas (median level=614 vs. 587 ng/L), although the test did not reach statistical significance (P=0.13). When adenoma number, size and histology were simultaneously included in the age-adjusted linear regression model, MIC-1 levels increased by 2.5% (95% CI, 0.4-4.7%, P=0.02) per each additional adenoma, and by 1.9% (95% CI, -0.8-4.7%,

P=0.16) per 1-cm increment of adenoma size (data only shown in the text). Histology of adenoma was not associated with MIC-1 levels. A gradual increase of MIC-1 levels was also observed from cases diagnosed with rectal, distal colon to proximal colon adenomas (median levels=568, 592 and 616 ng/L, respectively; *P*=0.12). Plasma CRP, IL-6 or sTNFR-2 levels did not differ by adenoma features.

Next, we assessed the association of MIC-1 with adenoma risk according to the pathologic characteristics (Table 5). We found that MIC-1 levels were statistically significantly related to an increased risk of adenomas with multiplicity (P_{trend}=0.02), large size (≥1cm, P_{trend}=0.03) or location in the proximal colon (P_{trend}=0.04). No statistically significant association was found for histologically more advanced adenomas or adenomas located in the distal colon or rectum.

Finally, we examined whether the association of MIC-1 with risk of adenoma varied by age and lifestyle factors (Supplementary Table 1). No statistically significant interaction was detected ($P_{interaction}$>0.30).

Discussion

In this prospective study nested within the NHS cohort, we found that compared to the lowest quintile, the highest quintile of plasma MIC-1, but not CRP, IL-6 or sTNFR-2, was positively associated with risk of advanced colorectal adenoma. This association appeared to be stronger for women with multiple, large adenomas and adenomas located in the proximal colon. Plasma MIC-1 level itself was also related to these diagnostic features among cases. Our results suggest that MIC-1 may be a biomarker for individuals at higher risk for colorectal neoplasia.

Although elevated CRP has been associated with higher CRC risk in a recent meta-analysis,(45) substantial heterogeneity was noted among studies. In contrary, several lines of evidence argue against a causal effect of CRP on CRC development. Circulating CRP levels were not associated with colonic mucosal measures of inflammation among healthy adults,(46) indicating that increased CRP in the circulation does not reflect colonic inflammation and the CRP-CRC association may be explained by other factors, such as reverse causation. In our previous study, the positive association between prediagnostic CRP and CRC risk was restricted to tumors diagnosed within the first 2 years after blood draw, and an essentially null association was found for cancers diagnosed after that time window.(24) This result suggests that increased CRP level in CRC patients may be not a cause but a consequence of systemic inflammation triggered by occult tumor initiation. Consistent with this hypothesis, none of the prospective studies, including our current one, found a positive association between CRP and risk of colorectal adenomas,(35-39) which are early precursor lesions for invasive cancer and thus less susceptible to the influence of reverse causation associated with tumor-induced inflammation.

For other inflammatory markers, evidence is sparse about their relationship to colorectal neoplasia. Consistent with our current findings, circulating IL-6 or sTNFR-2 was not associated with risk of CRC(10, 22-24, 26, 27) or adenoma(38) in previous studies, although

a positive association with CRC risk was detected for sTNFR-2 in the same cohort as the present study.(23) It is possible that TNF-α acts at a later stage of colorectal carcinogenesis that is not captured by examination of the first adenoma development among generally healthy women in the current study.

MIC-1 is a product of activated macrophages and a novel mediator in systemic inflammation.(28) High MIC-1 levels have been associated with an increased risk of cardiovascular disease,(47) all-cause mortality,(48) and cancers of the colorectum,(33, 34) pancreas,(30, 32) and prostate.(31) In the current study, we found that unlike CRP, IL-6 and sTNFR-2,MIC-1 levels were strongly associated with age, but not with BMI. This distinct correlate pattern suggests that unlike conventional cytokines, MIC-1 may represent a distinct class of marker for inflammation and other pathologic processes that accumulate over age and are less affected by metabolic changes. Interestingly, serum MIC-1 has been associated with aging-related cognitive decline after adjusting for other inflammatory markers (e.g., CRP, IL6, TNF-α).(49)

A progressive increase in serum MIC-1 levels has been observed between normal individuals, those with adenomatous polyps, and those with CRC,(33) suggesting a potential role of MIC-1 in the initiation and progression of colorectal tumors. In line with our results, serum MIC-1 concentrations rose with increasing numbers of adenomas and were positively associated with risk of recurrent colorectal adenomas in a prospective study with 3 years of follow-up.(40) These results corroborate the evidence base for the importance of MIC-1 throughout colorectal carcinogenesis. Building upon these findings, we also observed that MIC-1 was strongly associated with risk of large and multiple adenomas at diagnosis, although this association was observed primarily only in comparisons of the extreme quantiles. Moreover, the median time period between blood draw and adenoma diagnosis in our study was about 10 years and we observed similar results by either excluding cases diagnosed within 4 years after blood draw or restricting the cohort to individuals with a negative endoscopy prior to blood draw. These findings support an association of high MIC-1 level with the earliest stages of neoplasia development, including possibly tumor initiation. In addition, we found that the positive association between MIC-1 and adenoma risk was restricted to proximal colon adenoma, and MIC-levels increased among individuals eventually diagnosed with rectal, distal colon, and up to proximal colon adenomas. The potential for MIC-1 to serve as a biomarker for individuals at future risk of colorectal neoplasia, particularly for tumors in the proximal colon which are more challenging to detect endoscopically, requires further investigation.(50)

Despite the strong linkage of MIC-1 expression to tumors, little is known about its role in carcinogenesis. Some evidence suggests that MIC-1 possesses both tumorigenic and antitumorigenic activity.(29) MIC-1 induces apoptosis via both p53-dependent and p53-independent mechanisms,(51, 52) and modulates tumor growth, possibly through its activity on NSAID-mediated cell cycle arrest.(53, 54) Recently, paracrine effects of MIC-1 expression in fibroblasts were shown to promote prostate tumor growth and invasion.(55) Therefore, the dual effect of MIC-1 on tumor development is likely a function of the nature of the tumor and the interaction between tumor and its local microenvironment.(29) Elevated MIC-1 may represent a marker of host antitumor immune reaction to limit tumor

growth during an early stage of carcinogenesis, but when such protective mechanisms fail, the local production of MIC-1 from evolving tumors may serve as a pro-growth signal to facilitate tumor progression.(56)

Some limitations of our study need to be noted. First, a single measurement of plasma markers was available that may not represent their long-term levels. However, given the prospective matched design, measurement error is unlikely to differ between cases and controls, and thus can only attenuate our observed associations. Second, our analysis was focused only on women and limited largely to Caucasians. Therefore, our findings may not be generalizable to men or other ethnic populations. Third, we cannot establish whether MIC-1 plays a causal role in carcinogenesis or is primarily a biomarker for etiological pathways associated with the initiation or progression of neoplasia. Lastly, given the case-control design, our study is unable to assess the predictive capability of MIC-1 for screening. For this purpose, further prospective studies estimating the sensitivity and specificity of MIC-1 for neoplasia within a clinical screening program are needed. However, our study does provide proof-of-principle of the potential importance of chronic inflammation in the etiopathogenesis of CRC, including the development of early neoplasia (adenoma).

Our study has several strengths, including its prospective design, high follow-up rate over 18 years, detailed data on potential risk factors for both colorectal neoplasia and inflammation, and analysis of incident adenomas with confirmed diagnostic information. In particular, measures of plasma markers taken long before adenoma diagnosis minimize potential bias by early systemic alterations associated with neoplasia.

In conclusion, in this prospective study of US women, elevated levels of plasma MIC-1 was associated with higher risk of advanced colorectal adenomas, especially multiple adenomas and adenomas with large size and location in the proximal colon. In contrast, we did not find evidence for an association of CRP, IL-6 or sTNFR-2 with advanced colorectal adenomas. In addition, increasing adenoma number, size and more proximal location was directly associated with increasing MIC-1 levels. Our results provide further support for the role of MIC-1 in colorectal carcinogenesis and suggest the potential use of MIC-1 to improve the detection of advanced premalignant lesions during colorectal cancer screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AHEI	Alternate Healthy Eating Index
BMI	body mass index
CI	confidence interval
CRC	colorectal cancer
CRP	C-reactive protein
FFQ	food frequency questionnaire
GDF15	growth differentiation factor 15
IL-6	interleukin-6
MET	metabolic equivalent
MIC-1	macrophage inhibitory cytokine-1
NHS	Nurses' Health Study
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
sTNFR-2	soluble tumor necrosis factor receptor 2
TGF	transforming growth factor
TNF	tumor necrosis factor
TNFRSF1B	TNF receptor superfamily member 1B

Table 1

Baseline characteristics of participants in the Nurses' Health Study (1990)[a]

Variable	Cases (n = 757)	Controls (n = 757)	*P*
Age at blood draw, year	56.9 (6.8)	56.8 (6.7)	0.24
Body mass index, kg/m^2	25.9 (4.7)	25.4 (4.5)	0.01
Physical activity, MET-hours/week	14.7 (16.8)	16.9 (25.2)	0.14
Colorectal cancer in a parent or sibling, %	17	15	0.20
History of lower gastrointestinal endoscopy, %	33	32	0.61
Postmenopausal, %	84	84	0.70
Current use of menopausal hormone therapy, %[b]	42	48	0.09
Current multivitamin use, %	37	38	0.60
Regular aspirin use (≥2 tablets/week), %[c]	39	43	0.14
Regular NSAID use (≥2 tablets/week), %[d]	19	21	0.36
Current smoker, %	14	10	0.01
Alcohol consumption, g/d	5.6 (10.2)	4.9 (8.6)	0.78
Calcium intake, mg/d	1001 (519)	1035 (484)	0.06
Dietary AHEI score	44.0 (9.1)	45.0 (8.9)	0.03
Plasma biomarker levels, median (IQR)[e]			
MIC-1, ng/L	609 (494-783)	595 (488-741)	0.04
CRP, mg/L	1.91 (0.90-4.04)	1.56 (0.75-3.62)	0.01
IL-6, ng/L	0.96 (0.62-1.59)	0.96 (0.59-1.58)	0.55
sTNFR-2, μg/L	2.68 (2.30-3.16)	2.64 (2.30-3.10)	0.07
Time of diagnosis since blood draw, month	118 (57)	-	
Size of adenoma, mm	14.4 (9.8)	-	
Multiple (≥2) adenoma, %	34	-	
Adenoma location, %			
Proximal colon	28	-	
Distal colon	41	-	
Rectum	13	-	
Multiple adenomas in ≥2 locations	18	-	
Histology of adenoma, %			
Tubular	38	-	
Tubulovillous, villous or high-grade dysplasia (CIS)	62	-	

Abbreviations: AHEI, Alternative Healthy Eating Index; CIS, carcinoma in situ; CRP, C-reactive protein; IL-6, interleukin-6; IQR, inter-quartile range; MET, metabolic equivalent; MIC-1, macrophage inhibitory cytokine-1; NSAID, non-steroidal anti-inflammatory drug; sTNFR-2, soluble tumor necrosis factor receptor 2.

[a] Mean (standard deviation) is presented for continuous variables unless otherwise specified.

[b] Percentage is among postmenopausal women only.

[c] Regular use is defined as ≥2 standard (325-mg) tablets of aspirin per week.

[d] Regular use is defined as ≥2 tablets of NSAIDs per week.

[e]The number of pairs of subjects with missing measurements: 19 for MIC-1, 3 for CRP, and 24 for IL-6.

Table 2

Spearman correlation coefficient of plasma inflammatory marker levels with age and lifestyle factors among control participants in the Nurses' Health Study (1990)

Variable	MIC-1	CRP	IL-6	sTNFR-2	Age	BMI	Physical activity	Pack-years of smoking	Alcohol consumption	Dietary AHEI score
MIC-1	1	0.19 [a]	0.30 [a]	0.38 [a]	0.48 [a]	0.04	0.02	0.13 [a]	-0.06	0.05
CRP		1	0.41 [a]	0.38 [a]	0.22 [a]	0.38 [a]	-0.07 [c]	0.10 [a]	-0.05	-0.10 [a]
IL-6			1	0.38 [a]	0.21 [a]	0.27 [a]	-0.06	0.05	-0.12 [b]	-0.12 [b]
sTNFR-2				1	0.26 [a]	0.24 [a]	-0.06	0.05	-0.15 [a]	-0.10 [b]
Age					1	0.07	0.06	0.09 [c]	0.04	0.20 [a]
BMI						1	-0.10 [b]	0.02	-0.10 [b]	-0.12[b]
Physical activity							1	0.01	0.17 [a]	0.29 [a]
Pack-years of smoking								1	0.28 [a]	0.05
Alcohol consumption									1	0.21 [a]
Dietary AHEI score										1

Abbreviations: AHEI, Alternative Healthy Eating Index; BMI, body mass index; CRP, C-reactive protein; IL-6, interleukin-6; MIC-1, macrophage inhibitory cytokine-1; sTNFR-2, soluble tumor necrosis factor receptor 2.

[a] $P<0.001$.

[b] $0.001 \leq P<0.01$.

[c] $0.01 \leq P<0.05$.

Table 3

Risk of advanced colorectal adenoma according to quintiles of plasma inflammatory marker levels in the Nurses' Health Study (1990-2008)[a]

Biomarker	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
MIC-1						
Median, ng/L	398	505	596	707	951	
No. of cases/controls	131/148	150/148	131/147	145/148	181/147	
Age-adjusted OR (95% CI)[b]	1.00 (referent)	1.19 (0.86-1.64)	1.06 (0.75-1.49)	1.17 (0.83-1.65)	1.52 (1.06-2.18)	0.03
MV-adjusted OR (95% CI)[c]	1.00 (referent)	1.20 (0.86-1.68)	1.00 (0.70-1.42)	1.13 (0.79-1.63)	1.49 (1.01-2.18)	0.05
MV-adjusted OR (95% CI)[d]	1.00 (referent)	1.19 (0.84-1.67)	1.01 (0.70-1.44)	1.10 (0.76-1.60)	1.55 (1.03-2.32)	0.04
CRP						
Median, mg/L	0.43	0.91	1.70	2.99	6.32	
No. of cases/controls	127/150	137/152	131/151	169/151	190/150	
Age-adjusted OR (95% CI)[b]	1.00 (referent)	1.06 (0.77-1.47)	1.04 (0.75-1.46)	1.32 (0.96-1.83)	1.49 (1.09-2.05)	0.06
MV-adjusted OR (95% CI)[c]	1.00 (referent)	1.00 (0.71-1.40)	0.96 (0.68-1.36)	1.15 (0.81-1.63)	1.26 (0.89-1.79)	0.21
MV-adjusted OR (95% CI)[d]	1.00 (referent)	0.93 (0.66-1.33)	0.95 (0.66-1.36)	1.10 (0.77-1.59)	1.10 (0.76-1.59)	0.62
IL-6						
Median, ng/L	0.42	0.67	0.96	1.42	2.64	
No. of cases/controls	126/147	183/147	121/146	148/147	155/146	
Age-adjusted OR (95% CI)[b]	1.00 (referent)	1.49 (1.06-2.09)	0.97 (0.68-1.38)	1.18 (0.84-1.65)	1.23 (0.88-1.71)	0.59
MV-adjusted OR (95% CI)[c]	1.00 (referent)	1.33 (0.94-1.89)	0.79 (0.54-1.16)	0.93 (0.64-1.35)	0.99 (0.69-1.42)	0.64
MV-adjusted OR (95% CI)[d]	1.00 (referent)	1.33 (0.93-1.89)	0.77 (0.52-1.14)	0.91 (0.62-1.33)	0.96 (0.65-1.42)	0.53
sTNFR-2						
Median, μg/L	1.97	2.38	2.64	3.01	3.71	
No. of cases/controls	153/152	140/151	145/152	155/151	164/151	
Age-adjusted OR (95% CI)[b]	1.00 (referent)	0.92 (0.66-1.28)	0.96 (0.69-1.34)	1.03 (0.74-1.44)	1.10 (0.78-1.54)	0.41
MV-adjusted OR (95% CI)[c]	1.00 (referent)	0.86 (0.61-1.21)	0.91 (0.64-1.29)	0.92 (0.65-1.31)	0.99 (0.68-1.42)	0.83
MV-adjusted OR (95% CI)[d]	1.00 (referent)	0.86 (0.60-1.23)	0.90 (0.63-1.29)	0.88 (0.61-1.28)	0.89 (0.60-1.33)	0.69

Abbreviations: CI, confidence interval; CRP, C-reactive protein; IL-6, interleukin-6; MIC-1, macrophage inhibitory cytokine-1; MV, multivariable; OR, odds ratio; sTNFR-2, soluble tumor necrosis factor receptor 2.

[a] The number of pairs of subjects with missing measurements were excluded from the analysis: 19 for MIC-1, 3 for CRP, and 24 for IL-6.

[b] Age-adjusted models accounted for matching factors (date of endoscopy [i.e., had to be performed during the same 2-year period], birth year, indication for endoscopy, time period of any prior endoscopy, month and year of blood draw, and fasting status).

[c] Multivariable-adjusted models accounted for matching factors and were adjusted for family history of colorectal cancer (yes or no), multivitamin use (yes or no), pack-years of smoking before age 30 (0, 0-7.9, ≥8), alcohol consumption (0-0.14, 0.15-1.9, 2.0-7.4, ≥7.5 g/d), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (≤5, 5.1-10, 10.1-20, >20 MET-hours/week), regular aspirin/NSAID use (yes or no), postmenopausal status and hormone use (premenopausal, postmenopausal with ever or never using hormone therapy), calcium intake (in tertiles), and Alternative Healthy Eating Index (in tertiles).

[d] Multivariable-adjusted models were additionally adjusted for the other plasma markers omitting the main exposure (i.e., MIC-1, CRP, IL-6, and sTNFR-2).

Table 4

Median (inter-quartile range) levels of plasma inflammatory markers according to characteristics of colorectal adenoma among case participants in the Nurses' Health Study (1990)[a]

Characteristic	MIC-1, ng/L	CRP, mg/L	IL-6, ng/L	sTNFR-2, μg/L
Number of adenoma				
Single (n=482)	580 (485-742)	1.94 (0.92-3.86)	0.93 (0.62-1.62)	2.69 (2.32-3.13)
Multiple (n=252)	659 (517-856)	1.88 (0.78-4.45)	1.02 (0.62-1.58)	2.67 (2.26-3.22)
P value	<0.001	0.89	0.61	0.91
Size of adenoma				
<1 cm (n=114)	587 (474-772)	1.73 (0.84-3.60)	0.96 (0.65-1.50)	2.63 (2.37-3.03)
≥1 cm (n=613)	614 (497-783)	1.94 (0.90-4.07)	0.97 (0.62-1.59)	2.70 (2.29-3.18)
P value	0.13	0.47	0.84	0.58
Location				
Proximal colon (n=206)	616 (513-788)	2.08 (0.88-3.85)	0.91 (0.61-1.50)	2.71 (2.27-3.20)
Distal colon (n=298)	592 (480-753)	1.81 (0.88-4.04)	0.93 (0.60-1.50)	2.66 (2.33-3.09)
Rectum (n=98)	568 (487-759)	2.00 (1.21-3.71)	1.10 (0.67-1.93)	2.65 (2.26-3.10)
Multiple adenomas in ≥2 locations (n=131)	638 (508-823)	1.81 (0.75-4.46)	1.06 (0.62-1.57)	2.83 (2.32-3.33)
P value	0.12	0.79	0.16	0.30
Histological type				
Tubular adenoma (n=247)	612 (494-778)	2.00 (0.84-4.06)	0.93 (0.60-1.59)	2.72 (2.33-3.20)
Tubulovillous, villous adenoma or high-grade dysplasia (n=400)	607 (489-786)	1.88 (0.91-4.15)	0.99 (0.62-1.68)	2.67 (2.32-3.13)
P value	0.91	0.36	0.35	0.63

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6; MIC-1, macrophage inhibitory cytokine-1; sTNFR-2, soluble tumor necrosis factor receptor 2.

[a] Adenoma characteristics were missing for some cases and thus the total number of cases may not add up to 757.

Table 5

Odds ratio (95% confidence interval) of advanced colorectal adenomas according to quartiles of plasma MIC-1 levels by adenoma characteristics in the Nurses' Health Study (1990-2008)

Subgroup	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
Multiple adenoma					
No. of cases/controls[a]	50/56	46/59	58/62	98/75	
OR (95% CI)[b]	1.00 (referent)	0.88 (0.50-1.56)	1.06 (0.59-1.89)	1.75 (0.98-3.13)	0.02
Adenoma of ≥1 cm					
No. of cases/controls[a]	141/155	146/149	141/159	185/150	
OR (95% CI)[b]	1.00 (referent)	1.11 (0.79-1.56)	0.99 (0.69-1.41)	1.49 (1.02-2.18)	0.03
Proximal colon adenoma					
No. of cases/controls[a]	39/48	55/56	45/54	67/48	
OR (95% CI)[b]	1.00 (referent)	1.25 (0.70-2.23)	1.06 (0.54-2.05)	1.97 (1.01-3.84)	0.04
Distal colon adenoma					
No. of cases/controls[a]	82/74	67/78	72/78	77/68	
OR (95% CI)[b]	1.00 (referent)	0.80 (0.50-1.29)	0.82 (0.50-1.36)	1.02 (0.59-1.78)	0.76
Rectal adenoma					
No. of cases/controls[a]	25/29	28/23	16/20	29/26	
OR (95% CI)[b]	1.00 (referent)	1.49 (0.63-3.52)	0.87 (0.37-2.03)	1.28 (0.54-3.04)	0.82
Multiple adenomas in ≥2 locations					
No. of cases/controls[a]	30/31	22/28	33/30	46/42	
OR (95% CI)[b]	1.00 (referent)	0.76 (0.35-1.66)	0.97 (0.47-2.02)	1.12 (0.52-2.42)	0.55
Villous or tubulovillous adenoma or high-grade dysplasia					
No. of cases/controls[a]	100/108	91/91	87/95	122/106	
OR (95% CI)[b]	1.00 (referent)	1.08 (0.72-1.61)	1.00 (0.65-1.56)	1.29 (0.82-2.04)	0.26

Abbreviations: CI, confidence interval; MIC-1, macrophage inhibitory cytokine-1; OR, odds ratio.

[a] Adenoma characteristics were missing for some cases and thus the total number of cases may not add up to 757.

[b] Multivariable model accounted for matching factors (date of endoscopy [i.e., had to be performed during the same 2-year period], birth year, indication for endoscopy, time period of any prior endoscopy, month and year of blood draw, and fasting status) and was additionally adjusted for family history of colorectal cancer (yes or no), multivitamin use (yes or no), pack-years of smoking before age 30 (0,

0-7.9, ≥8), alcohol consumption (0-0.14, 0.15-1.9, 2.0-7.4, ≥7.5 g/d), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (≤5, 5.1-10, 10.1-20, >20 MET-hours/week), regular aspirin/NSAID use (yes or no), postmenopausal status and hormone use (premenopausal, postmenopausal with ever or never using hormone therapy), calcium intake (in tertiles), and Alternative Healthy Eating Index (in tertiles).