C-reactive protein and colorectal adenomas: Self Defense Forces Health Study

Toshie Otake,[1,2] Kousaku Uezono,[1,3] Ryota Takahashi,[1,3] Jin Fukumoto,[1] Shinji Tabata,[2] Hiroshi Abe,[2] Osamu Tajima,[1,3] Tetsuya Mizoue,[4] Keizo Ohnaka[5] and Suminori Kono[1,6]

[1]Department of Preventive Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka; [2]Self Defense Forces Fukuoka Hospital, Kasuga-shi; [3]Self Defense Forces Kumamoto Hospital, Kumamoto; [4]Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo; [5]Department of Geriatric Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

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Chronic inflammation has been implicated in colorectal carcinogenesis. Several studies have investigated the relationship between C-reactive protein (CRP), a biomarker of inflammation, and colorectal cancer and adenomas, resulting in inconsistent findings. The present study examined the relationship between circulating levels of high-sensitivity CRP and colorectal adenomas. The study subjects comprised 646 cases of colorectal adenoma and 635 controls of normal total colonoscopy among men receiving a preretirement health examination at two hospitals of the Self Defense Forces. Statistical adjustment was made for cigarette smoking, alcohol use, body mass index, physical activity, and other potential confounders. The multivariate-adjusted geometric means showed no measurable differences between adenoma cases and controls, but were higher among cases with larger adenomas (trend *P* = 0.03). Likewise, although the prevalence odds of colorectal adenomas did not differ according to CRP levels as categorized at the 30th, 60th, and 90th percentiles in the controls, higher levels of CRP were associated with a statistically significant increase in the prevalence odds of large adenomas (≥5 mm), but not of small adenomas (<5 mm). The multivariate-adjusted odds ratios of large adenomas for the lowest to highest categories of CRP were 1.00 (referent), 1.81 (95% confidence interval 1.17–2.80), 1.61 (95% confidence interval 1.03–2.52), and 2.21 (95% confidence interval 1.28–3.84), respectively (trend *P* = 0.01). A positive association between CRP and prevalence odds of large adenomas was not modified by either smoking or overweight. These findings suggest that inflammation is linked to the growth of colorectal adenomas. (*Cancer Sci* 2009; 100: 709–714)

Chronic inflammation has been implicated in carcinogenesis.[1,2] Inflammatory cytokines are considered to promote carcinogenesis by inducing oxidative DNA damage, stimulating cell proliferation and angiogenesis, and inhibiting apoptosis.[1,2] Particular interest has been drawn to the role of inflammation in colorectal carcinogenesis. Chronic inflammatory bowel diseases are known to confer increased risk of colorectal cancer,[3,4] and use of aspirin or non-steroidal anti-inflammatory drugs has consistently been related to reduced risk of colorectal adenomas and cancer in observational and intervention studies.[5–8] Recently, several prospective studies have investigated the relationship between C-reactive protein (CRP), a biomarker of inflammation, and colorectal cancer risk, resulting in inconsistent findings.[9–16] An increased risk of colorectal cancer associated with increased concentrations of CRP was first reported in the CLUE II study.[9] A positive association between CRP and colorectal caner risk was replicated in three subsequent studies,[10–12] but no such association was observed in four other studies.[13–16] One of the latter studies even suggested a decreased risk associated with high concentrations of CRP.[13] Results are also inconsistent regarding circulating CRP and colorectal adenomas, a well-known precursor lesion of colorectal cancer,[17,18] with one reporting a positive association[19] and another suggesting an inverse association.[20]

We investigated the relationship between circulating levels of CRP and colorectal adenomas in the Self Defense Forces (SDF) Health Study. Because some of the previous studies reported that an increased risk of colorectal cancer associated with high levels of CRP was more evident in less obese individuals and non-smokers,[9,11] we also addressed the effect modifications of adiposity and smoking on the association between CRP and colorectal adenomas.

Materials and Methods

Study subjects. The study subjects were male officials who received a preretirement health examination (before April 2002) or a health check-up at the age of 50 years (since April 2002) at the SDF Fukuoka Hospital during the period from August 1997 to March 2004 or at the SDF Kumamoto Hospital from January 1997 to March 2004. Details of the health examination have been described elsewhere.[21–23] All study subjects gave written informed consent. The study was approved by the ethics committee of the Kyushu University Faculty of Medical Sciences.

The present study included 646 cases of colorectal adenoma and 635 controls of normal total colonoscopy. In the consecutive series of 5337 men, except for 47 who refused to participate in the study, 5174 (97%) underwent colonoscopy. A total of 1065 men were excluded for the following reasons: a prior history of malignant neoplasm ($n = 56$), colectomy ($n = 28$), inflammatory bowel disease ($n = 5$), colorectal polyps or polypectomy ($n = 1006$). Colonoscopic findings were classified as normal ($n = 2156$), colorectal polyps ($n = 1619$), carcinoma ($n = 2$), and non-polypoid benign lesions ($n = 332$). Of the 1619 with colorectal polyps, 678 were found to have at least one histologically confirmed adenoma without *in situ* or invasive carcinoma. Of the 2488 men with normal colonoscopy or non-polypoid benign lesions, 2247 who underwent total colonoscopy were control candidates. Of them, 678 men were randomly selected by frequency matching with respect to hospital. Blood samples were not available for 22 cases and 30 controls, and CRP was measured for 656 cases and 648 controls. We further excluded 10 cases and 13 controls with CRP of >10 000 ng/mL, because such high values are probably indicative of clinically relevant inflammatory conditions.[24]

Colonoscopy. Colonoscopy was a routine procedure in the health examinations, and was carried out by expert or experienced endoscopists at each hospital. Histological diagnosis of biopsied or polypectomized specimens was referred to the pathology department of a university hospital at the Fukuoka Hospital and external pathology laboratories at the Kumamoto Hospital. Endoscopy

[6]To whom correspondence should be addressed.
E-mail: skono@phealth.med.kyushu-u.ac.jp

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and pathology reports were reviewed to record the number of polyps, location and size of each polyp, histological type, and atypia grade. Tubular, tubulovillous, or villous adenoma was classified as an adenoma.

Laboratory methods. A sample of 7 mL venous blood was obtained after an overnight fast for the purpose of medical research. Aliquots of plasma (January 1997 to March 2002) or serum (April 2002 to March 2004) were stored at –80°C until analysis. Concentrations of high-sensitivity CRP were measured at an external laboratory (SRL, Hachiohji, Japan) by using a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Marburg, Germany).[25] The limit of detection was 50 ng/mL, and a value of 25 ng/mL was assigned when the value was lower than the detection limit.

Lifestyle and clinical data. A self-administered questionnaire was used to assess smoking habits, alcohol intake, physical activity, other lifestyle characteristics, and parental disease histories. Lifetime exposure to cigarette smoking was expressed as cigarette-years (the average number of cigarettes smoking per day multiplied by years of smoking), and classified into 0, 1–399, 400–799, and ≥800 cigarette-years. Habitual alcohol drinking was defined as having drunk alcoholic beverages at least once per week for 1 year or longer, and former alcohol use was separated from current use. Alcohol intake was estimated for current drinkers on the basis of consumption frequencies and amount of five different alcoholic beverages (sake, shochu, beer, whiskey or brandy, and wine) on average in the past year. Alcohol use was categorized into never, former, and current use with a consumption of <30, 30–59, or ≥60 mL of ethanol per day. With regard to leisure-time physical activity, individuals reported types of regular exercise together with weekly frequency and time spent per occasion for each activity. Reported type of exercise was classified into four activities in terms of metabolic equivalent (MET). The reported time spent in each activity was multiplied by the corresponding MET value (light 2, moderate 4, heavy 6, and very heavy 8) to yield a MET-hour score per week. Individuals were classified into four groups, <5, 5–14, 15–29, and ≥30 MET-hours/week, with the cut-off points roughly corresponding to quartiles in the control group.

Body mass index (kg/m^2) was calculated as a measure of obesity. Body mass index was divided into four categories, <22.5, 22.5–24.9, 25.0–27.4, and ≥27.5 kg/m^2. Parental history of colorectal cancer was also elicited. Three men (two cases and one control) with unknown parental history of colorectal cancer were regarded as having no such history.

Statistical analysis. Comparison of means, medians, and proportions between cases and controls was done by *t*-test, Wilcoxon rank-sum test, and χ^2-test, respectively. The distribution of CRP concentrations was skewed to the right, and natural logarithms of these values were used to obtain means for controls and cases of adenomas, with and without allowance for adenoma size, by analysis of covariance. Increasing (or decreasing) trend of mean concentrations of CRP with respect to adenoma size was tested by multiple linear regression analysis with ordinal values assigned to categories by adenoma size. Logistic regression analysis was used to obtain odds ratios (OR) of colorectal adenomas according to CRP levels, and 95% confidence intervals (CI) were derived from standard errors of the logistic regression coefficients. Individuals were classified according to CRP concentrations by using the 30th, 60th, and 90th percentiles in the controls as cut-off points. Statistical adjustment was always made for age in years, hospital, and plasma and serum status, and further adjustment was made for rank in the SDF (low, middle, and high), cigarette smoking, alcohol use, body mass index, physical activity, and parental colorectal cancer. Indicator variables representing categories of the above-mentioned covariates were included in the models as independent variables. Trend of the association between CRP and adenomas was assessed with ordinal values assigned to the four categories of CRP in order. In testing interactions between CRP and either smoking or adiposity, a cross-product term was created by using the ordinal value for CRP (four categories) and a two-category term for heavy smoking (≥400 cigarette-years) or overweight (body mass index ≥25.0). Statistical significance for the interaction was tested using the likelihood ratio test comparing the logistic models with and without the interaction term. All statistical tests were two-sided, and statistical significance was declared if *P*-values were <0.05 or if 95% CI did not include unity. All analyses were conducted using the Statistical Analysis System, version 8.2 (SAS Institute, Cary, NC, USA).

Results

Selected characteristics of the cases and controls are summarized in Table 1. Age was slightly, but statistically significantly, higher in the cases than in the controls. Exposure to cigarette smoking and alcohol use were also statistically significantly greater in the cases. Leisure-time physical activity tended to be lower in the cases, whereas there was no difference in body mass index between the two groups. CRP concentration was higher in the cases.

Table 1. Selected characteristics of adenoma cases and controls

Characteristic	Cases (n = 646)	Controls (n = 635)	*P*-value[†]
Age (years), mean (SD)	52.0 (1.4)	51.8 (1.5)	0.03
Hospital (%)			0.79
Fukuoka	68.4	67.7	
Kumamoto	31.6	32.3	
Rank in the Self Defense Forces (%)			0.60
Low	62.5	64.7	
Middle	21.4	21.1	
High	16.1	14.2	
Cigarette-years, median (IQR)	580 (200–680)	300 (0–600)	<0.0001
Alcohol use (ml/day), median (IQR)	41 (15–66)	35 (12–63)	0.03
MET-hours/week[‡], median (IQR)	13 (2–26)	16 (5–27)	0.15
Body mass index (kg/m^2), mean (SD)	24.1 (3.0)	24.1 (2.7)	0.70
Parental colorectal cancer (%)	5.0	5.2	0.84
CRP (ng/mL), median (IQR)	391 (211–792)	348 (182–712)	0.04

CRP, C-reactive protein; IQR, interquartile range; MET, metabolic equivalent; SD, standard deviation.
[†]Comparisons of means, proportions, and medians were based on unpaired *t*-test, χ^2 test, and Wilcoxon rank-sum test, respectively.
[‡]Leisure-time physical activity.

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Table 2. Circulating levels of C-reactive protein and colorectal adenomas

Site of adenoma		C-reactive protein (ng/mL)				Trend
		<206	206–458	459–1540	≥1541	
Colorectum	No.†	157/191	205/190	211/191	73/63	
	OR (95% CI)‡	1.00 (referent)	1.30 (0.97–1.74)	1.34 (1.00–1.79)	1.38 (0.92–2.06)	$P = 0.052$
	OR (95% CI)§	1.00 (referent)	1.31 (0.97–1.78)	1.19 (0.87–1.63)	1.15 (0.75–1.75)	$P = 0.46$
Colon	No.†	126/191	161/190	171/191	60/63	
	OR (95% CI)‡	1.00 (referent)	1.28 (0.94–1.75)	1.36 (1.00–1.85)	1.44 (0.94–2.20)	$P = 0.04$
	OR (95% CI)§	1.00 (referent)	1.29 (0.93–1.78)	1.21 (0.87–1.69)	1.18 (0.76–1.84)	$P = 0.38$
Proximal colon	No.†	53/191	76/190	60/191	23/63	
	OR (95% CI)‡	1.00 (referent)	1.44 (0.96–2.17)	1.11 (0.72–1.69)	1.27 (0.72–2.26)	$P = 0.60$
	OR (95% CI)§	1.00 (referent)	1.44 (0.95–2.20)	1.02 (0.65–1.59)	1.06 (0.58–1.94)	$P = 0.88$
Distal colon	No.†	57/191	72/190	93/191	27/63	
	OR (95% CI)‡	1.00 (referent)	1.28 (0.85–1.91)	1.66 (1.13–2.45)	1.47 (0.85–2.54)	$P = 0.02$
	OR (95% CI)§	1.00 (referent)	1.28 (0.84–1.95)	1.47 (0.97–2.22)	1.22 (0.69–2.16)	$P = 0.19$
Rectum	No.†	24/191	34/190	18/191	9/63	
	OR (95% CI)‡	1.00 (referent)	1.40 (0.80–2.45)	0.71 (0.37–1.35)	1.06 (0.47–2.41)	$P = 0.47$
	OR (95% CI)§	1.00 (referent)	1.52 (0.84–2.76)	0.68 (0.34–1.36)	1.03 (0.43–2.46)	$P = 0.42$

CI, confidence interval; OR, odds ratio.
†Numbers of cases/controls.
‡Adjusted for age, hospital, and plasma/serum status.
§Adjusted for age, hospital, plasma/serum status, rank in the Self Defense Forces, cigarette smoking, alcohol use, body mass index, physical activity, and parental colorectal cancer.

Table 3. Circulating levels of C-reactive protein and colorectal adenomas by size of adenoma

Size of adenoma		C-reactive protein (ng/mL)				Trend
		<206	206–458	459–1540	≥1541	
Large (≥5 mm)	No.†	46/191	82/190	83/191	40/63	
	OR (95% CI)‡	1.00 (referent)	1.88 (1.24–2.86)	1.88 (1.23–2.85)	2.70 (1.60–4.55)	$P = 0.0002$
	OR (95% CI)§	1.00 (referent)	1.81 (1.17–2.80)	1.61 (1.03–2.52)	2.21 (1.28–3.84)	$P = 0.01$
Small (<5 mm)	No.†	108/191	122/190	126/191	33/63	
	OR (95% CI)‡	1.00 (referent)	1.12 (0.81–1.56)	1.15 (0.83–1.60)	0.91 (0.56–1.48)	$P = 0.83$
	OR (95% CI)§	1.00 (referent)	1.18 (0.84–1.66)	1.06 (0.75–1.51)	0.77 (0.46–1.28)	$P = 0.55$

CI, confidence interval; OR, odds ratio.
†Numbers of cases/controls.
‡Adjusted for age, hospital, and plasma/serum status.
§Adjusted for age, hospital, plasma/serum status, rank in the Self Defense Forces, cigarette smoking, alcohol use, body mass index, physical activity and, parental colorectal cancer.

The numbers of cases with colon adenomas only, rectal adenomas only, and adenomas at both sites were 518, 85, and 43, respectively. Cases of adenoma <5, 5–9, ≥10 mm, and unknown in size numbered 389, 200, 51, and 6, respectively. The size of the largest adenoma was used as the adenoma size for cases having multiple adenomas. Adenoma ≥5 mm in size was defined arbitrarily as large adenoma because cases with adenoma ≥10 mm were few. Cases with tubulovillous or villous adenoma numbered 17, and adenoma of severe atypia was detected in 13 cases. Multiple adenoma was found in 178 cases, and advanced adenoma (≥10 mm in size, tubulovillous/villous adenoma or severe atypia) was present in 73 cases.

With adjustment for age, hospital, and plasma and serum status, geometric means of CRP concentrations were 417 ng/mL (95% CI 384–453) in cases and 370 ng/mL (95% CI 340–402) in controls ($P = 0.045$). The corresponding values did not show a statistically significant difference between cases and controls after further adjustment for the remaining covariates; geometric means for cases and controls were 402 (95% CI 371–434) and 384 ng/mL (95% CI 355–416), respectively ($P = 0.44$). In the analysis allowing for adenoma size (<5, 5–9, and ≥10 mm), multivariate-adjusted geometric means of CRP for controls and cases with adenoma of <5, 5–9, and ≥10 mm were 384, 369, 453, and 511 ng/mL, respectively (trend $P = 0.03$).

The prevalence odds of colorectal adenomas increased with increasing levels of CRP showing a nearly significant trend ($P = 0.052$) when adjustment was limited to age, hospital, and plasma/serum status (Table 2). With full adjustment for the covariates, however, the positive association disappeared. Much attenuation was ascribed to the adjustment for cigarette-smoking. After adjustment for smoking in addition to age, hospital, and plasma/serum status, the OR of colorectal adenomas for the lowest to highest categories of CRP were 1.00 (referent), 1.29 (95% CI 0.96–1.73), 1.20 (0.89–1.61), and 1.19 (0.79–1.79), respectively (trend $P = 0.34$). Likewise, circulating CRP showed a weak positive association with colon adenomas (trend $P = 0.04$), particularly with distal colon adenomas (trend $P = 0.02$), but not with rectal adenomas, which was almost nullified after the full adjustment.

When the analysis was done for large (≥5 mm) and small (<5 mm) adenomas separately (Table 3), circulating levels of CRP were positively associated with the prevalence odds of large adenomas showing a highly significant trend ($P = 0.0002$), and the positive association remained statistically significant even after full adjustment for the covariates (trend $P = 0.01$). A slight

Table 4. Circulating levels of C-reactive protein and colorectal adenomas with stratification by cigarette smoking

Cigarette-years		C-reactive protein (ng/mL)				Trend
		<206	206–458	459–1540	≥1541	
All adenomas						
<400	No.†	68/119	90/112	66/86	19/24	
	OR (95% CI)‡	1.00 (referent)	1.39 (0.91–2.10)	1.30 (0.82–2.05)	1.30 (0.65–2.60)	$P = 0.77$
≥400	No.†	89/72	115/78	145/105	54/39	
	OR (95% CI)‡	2.04 (1.31–3.18)	2.54 (1.66–3.89)	2.32 (1.54–3.49)	2.20 (1.30–3.71)	$P = 0.57$
Large adenomas						
<400	No.†	20/119	32/112	25/86	12/24	
	OR (95% CI)‡	1.00 (referent)	1.73 (0.92–3.25)	1.72 (0.87–3.38)	3.14 (1.31–7.54)	$P = 0.06$
≥400	No.†	26/72	50/78	58/105	28/39	
	OR (95% CI)‡	2.02 (1.03–3.98)	3.86 (2.09–7.13)	3.20 (1.75–5.86)	3.73 (1.84–7.58)	$P = 0.07$
Small adenomas						
<400	No.†	47/119	58/112	41/86	7/24	
	OR (95% CI)‡	1.00 (referent)	1.30 (0.81–2.08)	1.20 (0.71–2.02)	0.70 (0.28–1.76)	$P = 0.46$
≥400	No.†	61/72	64/78	85/105	26/39	
	OR (95% CI)‡	2.00 (1.23–3.28)	2.10 (1.30–3.41)	1.98 (1.25–3.14)	1.58 (0.85–2.92)	$P = 0.76$

CI, confidence interval; OR, odds ratio.
†Numbers of cases/controls.
‡Adjusted for age, hospital, plasma/serum status, rank in the Self Defense Forces, alcohol use, body mass index, physical activity, and parental colorectal cancer.
P-values for interaction were 0.51 (all adenomas), 0.32 (large adenomas), and 0.69 (small adenomas).

attenuation in the multivariate-adjusted OR was largely ascribed to the control for smoking and body mass index. The OR for the lowest to highest categories of CRP after adjustment for age, hospital, plasma/serum status, and smoking were 1.00 (referent), 1.83 (95% CI 1.19–2.80), 1.65 (95% CI 1.08–2.53), and 2.35 (95% CI 1.38–4.02), respectively (trend $P = 0.0041$), and the corresponding OR after further adjustment for body mass index were 1.00 (referent), 1.79 (95% CI 1.16–2.76), 1.59 (95% CI 1.02–2.46), and 2.26 (95% CI 1.31–3.89), respectively (trend $P = 0.01$). A positive association with CRP of almost the same strength was observed for large adenomas exclusively located at the colon ($n = 181$); multivariate-adjusted OR for the lowest to highest categories of CRP were 1.00 (referent), 1.68 (95% CI 1.03–2.73), 1.39 (95% CI 0.84–2.29), and 2.13 (95% CI 1.16–3.90), respectively (trend $P = 0.047$). Cases of large rectal adenomas, with no adenoma at the other sites, were very few ($n = 39$), and a positive association with CRP was only suggestive; multivariate-adjusted OR for the lowest to highest categories of CRP were 1.00 (referent), 3.15 (95% CI 1.21–8.22), 1.16 (95% CI 0.38–3.47), and 2.98 (95% CI 0.91–9.77), respectively (trend $P = 0.35$).

Advanced adenomas also showed a statistically significant elevation in the prevalence odds at the highest category of CRP, but not showing a statistically significant trend, whereas there was only a weak positive, statistically non-significant association between CRP and multiple adenomas; multivariate-adjusted OR of advanced adenomas for the lowest to highest categories of CRP were 1.00 (referent), 1.42 (95% CI 0.70–2.88), 1.18 (95% CI 0.56–2.46), and 2.57 (95% CI 1.11–5.99), respectively (trend $P = 0.10$), and the corresponding OR of multiple adenomas were 1.00 (referent), 1.17 (95% CI 0.72–1.92), 1.28 (95% CI 0.79–2.08), and 1.55 (95% CI 0.84–2.86), respectively (trend $P = 0.15$).

Cigarette smoking was strongly, positively related to colorectal adenomas, with multivariate-adjusted OR for the categories of 0, 1–399, 400–799, and 800 cigarette-years of 1.00 (referent), 1.43 (95% CI 1.02–2.01), 2.03 (95% CI 1.51–2.73), and 2.66 (95% CI 1.83–3.88), respectively. The association with smoking did not differ by size of adenoma; the OR associated with heavy smoking (≥400 cigarette-years) were 2.00 (95% CI 1.46–2.75) for large adenomas and 1.74 (95% CI 1.33–2.27) for small adenomas. Body mass index was weakly, statistically non-significantly associated with large adenomas, but not with small adenomas; multivariate-adjusted OR of large and small adenomas associated with overweight (body mass index ≥25.0) were 1.29 (95% CI 0.94–1.77) and 1.17 (95% CI 0.89–1.53), respectively. The analysis was done to examine the effect modification of heavy smoking or overweight on the association of CRP concentrations with all adenomas and size-specific adenomas. No measurable interaction was observed for either heavy smoking (Table 4) or overweight (Table 5) regarding the prevalence odds of all adenomas and size-specific adenomas. A positive association between CRP and large adenomas was observed within each subgroup stratified by smoking or overweight, although the trend marginally failed to reach statistical significance. Nor did the site-specific analysis show measurable effect modifications of smoking and overweight on the relationship between CRP concentrations and either colon or rectal adenomas (data not shown).

Discussion

This cross-sectional study showed a positive association of circulating CRP with large colorectal adenomas, but not with small adenomas, independent of cigarette smoking, adiposity, and other factors. The findings suggest that inflammation is linked to the growth of colorectal adenomas.

Adiposity and smoking are strongly, positively correlated with circulating levels of CRP.[24] Expanded adipose tissue mass increases the secretion of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, and the signal to hepatic synthesis of CRP predominantly under control of interleukin-6 is enhanced.[26] Although the mechanisms by which smoking increases concentrations of CRP remain uncertain, increased concentrations of CRP in smokers are probably a reflection of vascular inflammation linked to atherosclerosis or due to systemic or non-vascular local inflammation.[27] Because these two factors are related to increased risk of colorectal adenomas,[28,29] they are deemed to be important confounders in the relationship between CRP and colorectal adenomas. Smoking was strongly associated with colorectal adenomas regardless of the size of adenoma in the present study, as observed previously in different datasets of the SDF Health Study.[30,31] On the other hand, body mass index was not as strongly associated with large adenomas in the present dataset as observed in an earlier study.[21] A modest increase in the prevalence odds

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Table 5. Circulating levels of C-reactive protein and colorectal adenomas with stratification by body mass index

Body mass index (kg/m²)		C-reactive protein (ng/mL)				Trend
		<206	206–458	459–1540	≥1541	
All adenomas						
<25.0	No.†	126/155	123/131	116/105	41/32	
	OR (95% CI)‡	1.00 (referent)	1.15 (0.81–1.63)	1.19 (0.82–1.72)	1.26 (0.74–2.17)	$P = 0.48$
≥25.0	No.†	31/36	82/59	95/86	32/31	
	OR (95% CI)‡	1.13 (0.65–1.96)	1.82 (1.19–2.77)	1.32 (0.90–1.95)	1.15 (0.65–2.02)	$P = 0.94$
Large adenomas						
<25.0	No.†	40/155	48/131	44/105	23/32	
	OR (95% CI)‡	1.00 (referent)	1.47 (0.89–2.41)	1.41 (0.84–2.36)	2.33 (1.18–4.61)	$P = 0.07$
≥25.0	No.†	6/36	34/59	39/86	17/31	
	OR (95% CI)‡	0.68 (0.26–1.78)	2.40 (1.35–4.27)	1.85 (1.07–3.19)	2.05 (1.00–4.22)	$P = 0.12$
Small adenomas						
<25.0	No.†	83/155	74/131	71/105	18/32	
	OR (95% CI)‡	1.00 (referent)	1.06 (0.71–1.58)	1.12 (0.74–1.70)	0.87 (0.45–1.68)	$P = 0.94$
≥25.0	No.†	25/36	48/59	55/86	15/31	
	OR (95% CI)‡	1.32 (0.73–2.40)	1.64 (1.01–2.65)	1.11 (0.71–1.73)	0.78 (0.39–1.56)	$P = 0.21$

CI, confidence interval; OR, odds ratio.
†Numbers of cases/controls.
‡Adjusted for age, hospital, plasma/serum status, rank in the Self Defense Forces, cigarette smoking, alcohol use, physical activity, and parental colorectal cancer.
P-values for interaction were 0.30 (all adenomas), 0.79 (large adenomas), and 0.17 (small adenomas).

of colorectal adenomas associated with higher concentrations of CRP was primarily due to the confounding effect of cigarette smoking. Adjustment for smoking and body mass index also slightly attenuated a positive association between CRP and large adenomas. On the other hand, the associations of smoking and body mass index with large adenomas did not change after inclusion of CRP in the model to such an extent that inflammation was implicated in these associations (data not shown).

Two recent studies reported conflicting results regarding CRP and colorectal adenomas.[19,20] A modest statistically non-significant increase in the prevalence odds was observed for the highest versus lowest third in the colonoscopy-based study at the University of North Carolina Hospitals.[19] In that study, much stronger positive associations were noted for interleukin-6 and tumor necrosis factor-α. In the latter study,[20] a nested case-control study in the CLUE II cohort,[9] higher concentrations of CRP were associated with a decreased rather than increased risk of colorectal adenomas. In the North Carolina study,[19] the median size of adenomas was 5 mm. Although it was reported that there was no statistically significant difference in CRP concentrations between large (≥10 mm) and small (<10 mm) adenoma cases, details were not described regarding the relationship between CRP concentrations and size-specific colorectal adenomas.[19] It was also reported in the CLUE II study that CRP concentrations in cases with large (≥10 mm) and small (<10 mm) adenomas each did not statistically significantly differ from those in controls.[20] It was thus a unique finding that circulating CRP was positively associated with only large adenomas. The present findings suggest that inflammation is more strongly linked to the growth of colorectal adenomas. Interestingly, aspirin use resulted in a much greater reduction in the recurrence of advanced adenomas than of non-advanced adenomas in one trial,[5] although no such difference was observed in another trial.[6]

Although the first report that circulating levels of CRP was associated with an increased risk of colorectal cancer in a prospective study of residents in Maryland[9] has subsequently been replicated in elderly men and women in the USA,[10] male smokers in Finland,[11] and middle-aged men and women in Japan,[12] no such association was observed in the Women's Health Study,[13] the Japan Collaborative Cohort Study,[14] the Rotterdam Study,[15] and the Greek component of the European Prospective Investigation into Cancer and Nutrition.[16] In all of these studies, CRP concentrations prior to the diagnosis of colorectal caner were determined by the so-called high-sensitive assay, and statistical adjustment was done for smoking, adiposity, and other potential confounders. It is not easy to find plausible reasons for these inconsistent findings. The small size of the study may be an explanation for the lack of a positive association in some studies. Except for a Japanese study,[12] most of these studies were based on less than 200 cases of colorectal cancer,[9,11,13–15] and the number of cases was less than 50 in two studies.[10,16] Inconsistency has also been noted regarding the site-specific association with CRP concentrations. An increased risk associated with elevated levels of CRP was confined to colon cancer in two studies,[9,12] whereas a positive association with CRP was stronger for rectal cancer than for colon cancer in one study.[11] In another study showing no association between CRP and the overall risk of colorectal cancer,[15] elevated concentrations of CRP were associated with a substantial decrease in the risk of rectal cancer and a suggestive increase in the risk of non-sigmoid colon cancer. A decreased risk of rectal cancer associated with higher concentrations of CRP was also noted in the Women's Health Study.[13] These disparate findings are probably ascribed to much smaller numbers of cases in the site-specific analysis. The present study did not substantiate a positive association between CRP and large rectal adenomas, although the findings were suggestive of such an association. Further studies are needed to clarify whether circulating CRP is differentially related to site-specific colorectal cancer and adenomas.

An increased risk of colorectal cancer associated with higher concentrations of CRP was greater in non-smokers in the CLUE II cohort.[9] In the present study, there was no material difference in the association between CRP and large adenomas between low and high exposure to cigarette smoking. Lifelong non-smokers were relatively few in the present study population. Results from the repeated analysis of 42 cases of large adenomas and 205 controls among non-smokers did not indicate a stronger association with CRP. The multivariate-adjusted OR for the lowest to highest category of CRP concentrations were 1.00, 1.12, 1.62, and 1.95, respectively (trend $P = 0.26$). A positive association between CRP and colorectal cancer seemed to be limited to non-overweight or less obese individuals.[9,11] There was no effect modification of overweight on the positive association between CRP concentrations and large colorectal adenomas in the present study.

Causality for the observed positive association between CRP and large adenomas merits consideration in view of the cross-sectional nature of the present study. It is possible that growth of adenomas may enhance local inflammation and thus elevate circulating levels of CRP. The progressively higher concentrations of CRP with increasing size of adenomas in the present study may be regarded as indicative of such a reverse causality. It has been shown that increased levels of CRP are predictive of poor prognosis or survival in patients with colorectal cancer[32] and other types of cancers.[33,34] Although it is hypothesized that an enhanced inflammatory response of the host to neoplastic foci may promote the growth or advance of neoplastic lesions,[10] a causal link between inflammation and growth of colorectal adenomas remains to be clarified.

Among the advantages in the present study was non-selective colonoscopy in a defined population; confirmation of the absence of polyp lesions in the control subjects by total colonoscopy; and allowance for important confounding factors. The previous studies on circulating CRP and colorectal adenomas were based on much fewer cases: 242 cases and 631 controls in one study,[19] and 135 cases and 269 controls in the other study.[20] A fairly large size of the present study was another strength. In addition to the issue of reverse causality as discussed above, several limitations are noted in the present study. A limitation was that CRP was measured only at one point in time. Although CRP concentrations show little or no diurnal or seasonal variation,[35] long-term levels of CRP in the past would be more relevant to the prevalence of colorectal adenomas. Another weakness was the lack of information on use of aspirin or non-steroidal anti-inflammatory drugs, which is associated with decreased risk of colorectal adenomas and cancer.[5–8] Furthermore, the present study was based on routine colonoscopy practice. Endoscopic procedure and histological diagnosis were not standardized specifically. This may have caused misclassification regarding diagnosis of adenoma and definition of adenoma characteristics.

In conclusion, the relationship between concentrations of circulating CRP and colorectal adenomas was examined in middle-aged Japanese men. Higher levels of circulating CRP were associated with a statistically significant increase in the prevalence odds of large colorectal adenomas (≥5 mm), but not of small adenomas, independent of smoking, adiposity, and other potential confounders. Inflammation is probably linked to the growth of colorectal adenomas, but consolidation is needed in further studies.

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