

# A Prospective Study of Serum C-Reactive Protein and Colorectal Cancer Risk in Men

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## Abstract

**Chronic inflammation has been implicated in the etiology of colorectal cancer. C-reactive protein (CRP), a sensitive marker of inflammation, has been investigated with regard to colorectal cancer in only three previous studies, and the results from these investigations were inconsistent. We examined serum CRP levels in relation to colorectal cancer incidence in a nested case-control study within the Alpha Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, a cohort of 29,133 Finnish males enrolled from 1985 to 1988 with follow-up through April 2002. Colorectal cancer cases were ascertained by the Finnish Cancer Registry; this analysis included 130 cases of colorectal cancer (with available blood), which occurred between 1990 and April 30, 2002, and 260 matched controls. Baseline median CRP levels were ~25% higher among colorectal cancer cases (3.4 mg/L) than controls (2.6 mg/L;  $P = 0.04$ ). Relative to men in the lowest quartile of CRP concentration, men in the highest quartile had an odds ratio of 2.9 (95% confidence interval, 1.4-6.0) for developing colorectal cancer with a dose-response relationship supported ( $P_{\text{trend}} = 0.006$ ). The relation between CRP and incident colorectal cancer was modified by body mass index such that the association was stronger among lean individuals than in heavier individuals ( $P_{\text{interaction}} = 0.018$ ). These results support the notion that chronic low-grade inflammation is a marker for increased risk of colorectal cancer. (Cancer Res 2006; 66(4): 2483-7)**

## Introduction

Mounting evidence suggests that chronic inflammation is functionally involved in colorectal carcinogenesis. Among patients with idiopathic inflammatory bowel disease (IBD), colorectal cancer incidence rates increase progressively over time, reaching 19% after 30 years of disease (1). Conversely, habitual use of nonsteroidal anti-inflammatory drugs such as aspirin confers a 40% to 50% reduction in colorectal cancer risk (2). Laboratory data further supports a mechanistic link between inflammation and colorectal carcinogenesis; for example, precursor lesions of colorectal cancer often display inflammatory histologic features (3). The inflammatory response promotes carcinogenesis by damaging DNA (4), stimulating angiogenesis and cell proliferation,

and inhibiting apoptosis (5). The association between serum levels of C-reactive protein (CRP), a sensitive marker of inflammation, and colorectal cancer risk has been examined in three previous studies, yet existing data are inconsistent; with one study demonstrating a strong positive relation (6) and the other two reporting essentially null findings (7, 8).

To clarify and extend the current knowledge, we conducted a nested case-control study within the Alpha Tocopherol, Beta Carotene (ATBC) Cancer Prevention Study cohort to investigate the relationship between serum CRP concentration and colorectal cancer incidence. In addition, we addressed whether the association between CRP level and colorectal cancer differed by body size or colorectal cancer subsite.

## Materials and Methods

**Study sample.** Colorectal cancer cases and controls were identified among ATBC study participants, details of which have been published previously (9). Briefly, between 1985 and 1988, 29,133 eligible male smokers from southwest Finland were randomized to test whether supplements of  $\alpha$ -tocopherol or  $\beta$ -carotene reduced lung cancer incidence. Prior to randomization, all participants completed a self-administered 276-item food frequency questionnaire. Height and weight were measured by a trained nurse. Additional information on aspirin use was obtained from a questionnaire administered during the follow-up period to which 93% of participants responded.

Colorectal cancer cases were identified using the Finnish Cancer Registry, which has virtually 100% case ascertainment in Finland (10). To limit the potential influence of preclinical cancer on serum CRP levels, only cases diagnosed at least 5 years after baseline were included in the present analysis. In total, 130 incident cases of colorectal cancer were available for analysis. Controls were selected from participants of the ATBC study who were alive at the time the case subject was diagnosed and free from cancer (except non-melanoma skin cancer). Controls were matched to cases at a ratio of 2:1 by age at randomization ( $\pm 5$  years), date of baseline serum blood draw ( $\pm 30$  days), and intervention group ( $\alpha$ -tocopherol,  $\beta$ -carotene, both assignments, placebo).

**Laboratory and statistical methods.** CRP was measured in baseline serum samples blinded to case-control status, using a high-sensitivity latex particle enhanced immunoturbidometric assay (K-ASSAY CRP Ultra, Equal Diagnostics, Exton, PA). Quality control samples ( $n = 47$ ) were embedded within batches to test for assay reproducibility. The overall coefficient of variation for this assay was 6.3%.

The distributions of baseline characteristics between cases and controls were compared using Wilcoxon rank sum tests for continuous variables and  $\chi^2$  tests for categorical variables. CRP levels were categorized into quartiles based on the distribution among the controls. Generalized linear models were used to assess the association between potential risk factors for colorectal cancer and CRP level among controls. Odds ratios (OR) and 95% confidence intervals (95% CI) relating CRP levels to colorectal cancer incidence were estimated using conditional logistic regression. All models

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were adjusted for an *a priori* determined set of potential confounding variables including age, body mass index [BMI; defined as weight / (height)<sup>2</sup>], aspirin use, smoking duration (years), and usual number of cigarettes smoked per day. Tests for trend were calculated using a single ordinal variable corresponding to the median values for each CRP quartile. We evaluated effect modification of the CRP and colorectal cancer relation with BMI by entering a cross product term of continuous CRP and BMI into a multivariable model, the coefficient of which was evaluated with the Wald test, and with stratified analyses of CRP by low and high BMI categories, based on the median value of BMI among the controls.

Subsite-specific colorectal cancer risks were determined for colon cancer (ICD9 codes 153.1-4, 153.6 and 154.0) and rectal cancer (ICD9 code 154.1) separately. All hypothesis tests were two-sided with  $P < 0.05$  deemed statistically significant, and were done using SAS release 8.2 (SAS Institute, Inc., Cary, NC).

## Results

Case and control subjects did not differ significantly by age, BMI, smoking history, physical activity, or intake of major dietary items. Daily use of aspirin was more common among controls than cases ( $P = 0.002$ ). Median serum CRP levels were statistically significantly higher among cases (3.4 mg/L) compared with controls (2.6 mg/L;  $P = 0.04$ ). In addition, baseline  $\alpha$ -tocopherol levels were significantly lower in cases (11.3 mg/L) compared with controls (12.0 mg/L;  $P = 0.04$ ; Table 1). CRP concentrations were positively related to BMI ( $P_{\text{trend}} = <0.0001$ ), total cigarettes smoked per day ( $P_{\text{trend}} = 0.05$ ), and a personal history of coronary heart disease ( $P_{\text{trend}} = 0.03$ ). An inverse relation was found between CRP and baseline serum  $\beta$ -carotene ( $P_{\text{trend}} = 0.03$ ) and dietary intake of *n-3* fatty acids, specifically those of vegetable origin ( $P_{\text{trend}} = 0.01$ ; Table 2).

Relative to men in the lowest quartile of CRP concentration, men in the highest quartile had an almost 3-fold (OR, 2.9; 95% CI, 1.4-6.0) increased odds of developing colorectal cancer in a significant dose-response manner ( $P_{\text{trend}} = 0.006$ ; Table 3). We observed no change in the risk estimates following adjustment for other potential confounding variables such as family history of colorectal cancer, history of diabetes mellitus, coronary heart disease or rheumatoid arthritis, serum  $\alpha$ -tocopherol and  $\beta$ -carotene levels, and intakes of alcohol, *n-3* fatty acids, and fiber.

The association between CRP and incident colorectal cancer was modified by BMI such that the association was strongest among subjects in the lower BMI category (OR, 4.6; 95% CI, 1.9-10.7, comparing the upper quartile to the lower quartile) compared with those in the upper BMI category (OR, 2.0; 95% CI, 0.9-4.6, comparing the upper quartile to the lower quartile;  $P_{\text{interaction}} = 0.018$ ; Table 3). By anatomic subsite, the association between CRP level and colorectal cancer was stronger for rectal cancer (OR, 7.8; 95% CI, 2.2-28.1) than in colon cancer (OR, 1.8; 95% CI, 0.7-4.4), when comparing the upper quartile with the lower quartile, however, only 57 cases of rectal cancer were included in the study (data not shown). We observed no difference in the association between CRP and colorectal cancer risk following stratification by aspirin use, years of being a regular smoker or total cigarettes smoked per day, and intake of *n-3* fatty acids or serum  $\alpha$ -tocopherol or  $\beta$ -carotene (data not shown).

## Discussion

In this prospective study, we showed that increased serum CRP is predictive of subsequent enhanced colorectal cancer risk.

These data are consistent with the study by Erlinger et al. who found a positive association between CRP and incident colorectal cancer of similar magnitude and a stronger association among leaner individuals compared with heavier individuals (6). Our findings differ from those of Zhang et al. and Ito et al. who observed no association between CRP levels and colorectal cancer risk among subjects enrolled in the Women's Health Study and Japan Collaborative Cohort Study, respectively (7, 8).

Obesity has recently been described as an "inflammatory condition:" overweight and obese individuals have higher circulating levels of CRP and increased body mass engenders a proinflammatory environment (11). This observation generated the hypothesis that chronic inflammation may represent one potential mechanism that mediates the association between obesity and colorectal cancer. We showed that BMI modified the CRP-colorectal cancer relation whereby the positive association between CRP and colorectal cancer was stronger in lean versus heavier men. One possible explanation for this observation is the existence in leaner men of fewer adiposity-related etiologic exposures related to colorectal cancer risk (e.g., hyperinsulinemia), with more sensitive and specific detection of the CRP association resulting among them. This may also explain the differing relative risks we observed for rectal and colon cancers, given that obesity is not strongly associated with the former (12). Our primary hypothesis, that chronic inflammation in the colorectum is a risk factor for colorectal cancer is supported by our data. The lack of association among heavier men may reflect increased CRP levels that are elevated in response to adipokines such as interleukin-6 and tumor necrosis factor- $\alpha$  which are up-regulated in heavier individuals. Controls that fall into the heavier category will have higher CRP levels than the leaner controls, and in support of this, BMI is positively related with CRP levels among controls in this study. Thus, the differences in inflammation levels between cases and controls among heavier men may be masked by this phenomenon.

Our study is limited by the relatively modest number of cases overall and only one baseline measurement of CRP. However, CRP levels have been found to remain reasonably stable over time (13), suggesting that a single baseline measurement can be used to represent long-term levels (14-17). Because our study participants were apparently healthy at the time of enrollment, it is unlikely that the presence of undetected colorectal neoplasia at baseline contributed to the observed positive association between CRP levels and colorectal cancer incidence. We further minimized this potential bias by including only cases diagnosed after the first 5 years of follow-up. Although we lacked CRP data on cases diagnosed within the first 5 years of follow-up, exclusion of cases diagnosed up to 10 years of study entry did not materially change the risk estimates [i.e., OR for the top quartile versus the lowest quartile, 3.0 (95% CI, 1.1-5.3)]. An important extension of this work would be to investigate CRP levels in relation to premalignant colorectal adenoma, with a demonstrable association further supporting the causative role of chronic inflammation in colorectal carcinogenesis.

Because our study was conducted in a cohort of male smokers, the generalizability of our findings to a population that includes nonsmokers may be limited. Smoking is known to be associated with chronic inflammation and is consistent with other studies (18). Our results show that smoking is positively associated with CRP levels. Median CRP levels among the control subjects were

higher in our population compared with previous studies on CRP and colorectal cancer (6–8). However, the consistency of our data with those from the study by Erlinger et al. (6), which was conducted in a separate population of mixed gender and smoking status, indicates that raised CRP levels may be a predictor of colorectal cancer incidence among both smoking and nonsmoking individuals. In addition, the relation between CRP and colorectal cancer incidence did not vary across subgroups of men, defined by smoking duration and smoking intensity in our study. Interestingly, our results differed with those of Erlinger et al. (6) with regard to anatomic subsite. We detected a stronger association for rectal cancer compared with colon cancer, whereas the former report

reported the converse. Such differences based on subsite should be interpreted with caution due to the small number of cases overall (only 57 rectal cancers) in the current study.

It should be noted that although CRP is a highly sensitive marker of inflammation, it is nonspecific, and may reflect on-going inflammatory processes at any anatomic site. It is unlikely that other diseases which are associated with raised CRP levels substantially contributed to the association reported here, because adjustment for a history of coronary heart disease, rheumatoid arthritis, and lung emphysema resulted in virtually unaltered risk estimates. Our study lacked information on IBD which is associated with both inflammation and colorectal cancer. However,

**Table 1.** Baseline characteristics of the study population

Characteristic	Cases ( <i>n</i> = 130)	Controls ( <i>n</i> = 260)	<i>P</i> *
Age (y)	56 (53-61)	57 (53-59)	0.37
BMI (kg/m <sup>2</sup> )	26.0 (24.0-28.8)	26.1 (23.7-28.3)	0.65
Smoking history			
Total cigarettes per day	20 (13-25)	20 (15-25)	0.53
Smoking duration (y)	36 (30-41)	36 (31-40)	0.94
Medical history			
Family history of colorectal cancer (%)	2.6	3.1	0.82 <sup>†</sup>
Diabetes mellitus (%)	3.8	2.7	0.53 <sup>†</sup>
Coronary heart disease (%)	6.9	5.4	0.54 <sup>†</sup>
Lung emphysema (%)	5.4	4.6	0.74 <sup>†</sup>
Rheumatoid arthritis (%)	1.5	2.3	0.61 <sup>†</sup>
Prior daily aspirin use (%) <sup>‡</sup>	6.2	19.6	0.002 <sup>†</sup>
Physical activity			
Occupational			0.36 <sup>†</sup>
Sedentary (%)	13.0	15.0	
Light (%)	20.8	28.9	
Moderate (%)	20.8	17.3	
Heavy (%)	5.4	5.4	
Nonworking (%)	40.7	33.5	
Recreational			0.75 <sup>†</sup>
Light (%)	36.9	33.1	
Moderate (%)	56.2	59.6	
Heavy (%)	6.9	7.3	
Dietary intake			
Total energy (kcal/d)	2,756 (2,230-3,377)	2,767 (2,242-3,250)	0.81
Fiber (g/d)	24 (18-33)	37 (22-56)	0.58
Alcohol (g/d)	16 (4-29)	13 (4-25)	0.45
Folate (μg/d)	325 (200-450)	334 (217-451)	0.73
Calcium (mg/d)	1,324 (674-1974)	1,330 (713-1947)	0.62
<i>n</i> -3 fatty acids (FA; g/d)	2.1 (0.9-3.3)	2.1 (1.0-3.2)	0.59
Marine, <i>n</i> -3 FA (g/d)	0.4 (0.2-0.6)	0.4 (0.1-0.7)	0.64
Vegetable, <i>n</i> -3 FA (g/d)	1.6 (0.7-2.5)	1.7 (0.7-2.7)	0.56
<i>n</i> -6 fatty acids (g/d)	7.5 (0.5-14.5)	7.7 (1.8-13.6)	0.92
Baseline serum measurements			
Serum CRP level (mg/L)	3.4 (1.7-6.5)	2.6 (1.4-4.8)	0.04
Serum α-tocopherol (mg/L)	11.3 (7.9-14.7)	12.0 (8.3-15.7)	0.04
Serum β-carotene (μg/L)	159.0 (12.0-306.0)	182.0 (13.5-350.5)	0.07
Anatomic subsite			
Colon, <i>n</i> (%)	73 (56%)		
Rectum, <i>n</i> (%)	57 (44%)		

NOTE: All values are medians (interquartile range) unless otherwise indicated.

\**P* values derived from the Wilcoxon signed rank sum test unless otherwise indicated.

†*P* value derived from the  $\chi^2$  test.

‡Aspirin data available on 93% of the study participants.

**Table 2.** Association between CRP and covariates among controls at baseline

Variable	Quartile of CRP (mg/L)				P-trend
	0.2-1.4	1.5-2.6	2.7-4.8	4.9-49.5	
Age (y)	56.3 (0.48)	56.0 (0.50)	57.1 (0.49)	56.5 (0.50)	0.42
BMI (kg/m <sup>2</sup> )	24.5 (0.40)	26.4 (0.42)	26.2 (0.41)	27.9 (0.42)	<0.0001
Cigarettes per day	17.5 (0.9)	20.4 (1.0)	20.8 (0.9)	20.3 (0.9)	0.05
Smoking duration (y)	34.7 (0.8)	36.2 (0.9)	36.1 (0.9)	36.5 (0.9)	0.44
Prior daily aspirin use (%)*	12.4	20.2	10.5	20.6	0.35
Alcohol (g/d)	15.1 (2.6)	18.8 (2.7)	20.0 (2.6)	19.5 (2.7)	0.54
<i>n</i> -3 fatty acids (g/d)	2.5 (0.1)	2.2 (0.1)	2.4 (0.1)	2.0 (0.1)	0.03
Marine, <i>n</i> -3 FA (g/d)	0.4 (0.04)	0.5 (0.04)	0.6 (0.04)	0.5 (0.04)	0.21
Vegetable, <i>n</i> -3 FA (g/d)	2.0 (0.1)	1.7 (0.1)	1.8 (0.1)	1.6 (0.1)	0.01
<i>n</i> -6 fatty acids (g/d)	10.2 (0.7)	9.7 (0.7)	9.5 (0.7)	7.7 (0.7)	0.08
Fiber (g/d)	27.8 (1.2)	26.6 (1.2)	25.9 (1.2)	24.1 (1.2)	0.19
Energy (kcal/d)	2,996 (95)	2,720 (99)	2,879 (98)	2,727 (98)	0.14
Folate (μg/d)	362.2 (11.8)	334.3 (12.3)	350.5 (12.1)	329.1 (12.2)	0.19
Calcium (mg/d)	1,429 (63)	1,309 (65)	1,395 (64)	1,390 (65)	0.60
Serum α-tocopherol (mg/L)	11.4 (0.4)	12.6 (0.5)	13.0 (0.5)	12.8 (0.5)	0.05
Serum β-carotene (μg/L)	232.0 (17.5)	238.9 (18.2)	215.6 (17.9)	169.5 (18.1)	0.03
Moderate/heavy physical work (%)	29.4	21.7	21.4	23.2	0.36
Moderate/heavy physical recreation (%)	67.4	60.8	67.4	67.0	0.78
Family history of colorectal cancer (%)	1.4	1.3	1.2	4.4	0.18
History of coronary heart disease (%)	3.3	4.1	4.5	10.7	0.03
History of diabetes mellitus (%)	0	5.2	2.3	4.5	0.18
History of lung emphysema (%)	5.4	2.1	4.5	7.1	0.38

NOTE: Values are means (SE) unless otherwise specified. All nutrients were adjusted for energy intake using the residuals method.

\*Aspirin data only available for 93% of study participants.

given the low incidence rates of IBD in Finland at the time of the baseline blood draw (~three cases per 100,000 person-years; ref. 19), it is improbable that failure to account for this condition would have influenced the results.

In conclusion, CRP is a well-established, highly sensitive clinical gauge of inflammation, and this is the second study to report a strong, positive association between CRP and incident colorectal cancer. Our findings support the hypothesis that chronic

**Table 3.** Association between serum CRP level and subsequent colorectal cancer risk with stratification by BMI level

Quartile of CRP (mg/L)					
All colorectal cancers					
Quartile range	0.2-1.4	1.5-2.6	2.7-4.8	4.9-49.5	<i>P</i> -trend*
Quartile median	0.9	1.8	3.5	6.8	
<i>n</i> (case/control)	24/68	34/63	24/65	48/64	
OR (95% CI) <sup>†</sup>	1.0 (ref)	1.5 (0.8-2.7)	1.0 (0.5-1.9)	2.0 (1.1-3.7)	0.02
OR (95% CI) <sup>‡</sup>	1.0 (ref)	1.9 (1.0-3.8)	1.2 (0.6-2.6)	2.9 (1.4-6.0)	0.006
BMI level					
<26.1 kg/m <sup>†</sup>					
<i>n</i> (case/control)	17/49	16/33	8/30	26/20	
OR (95% CI) <sup>§</sup>	1.0	1.6 (0.7-3.9)	0.8 (0.3-2.1)	4.6 (1.9-10.7)	0.01
>26.1 kg/m <sup>‡</sup>					
<i>n</i> (case/control)	7/19	18/30	16/35	22/44	
OR (95% CI) <sup>§</sup>	0.9 (0.3-2.7)	2.2 (0.9-5.3)	1.6 (0.7-3.7)	2.0 (0.9-4.6)	0.43
<i>P</i> (interaction) for CRP × BMI = 0.018					

\**P*-trend based on continuous data.

<sup>†</sup> ORs adjusted for age only.

<sup>‡</sup> ORs adjusted for age, BMI, smoking duration (years), number of cigarettes smoked per day, and prior daily use of aspirin.

<sup>§</sup> ORs adjusted for age, smoking duration (years), number of cigarettes smoked per day, and prior daily use of aspirin.

inflammation is causally related to this disease. The utility of CRP assessment for the clinical prediction of colorectal cancer requires further attention, whereas studies that incorporate measurements of other inflammatory variables and cytokines may potentially be very useful in elucidating the inflammation–colorectal carcinogenesis relation.

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