The association between predicted inflammatory status and colorectal adenoma

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We developed a diet and lifestyle score based on high sensitivity C-reactive protein (hsCRP), and investigated its association with odds of adenoma. We performed stepwise linear regression to develop the predicted hsCRP score among 23,330 participants in the Health Examinee Study and examined its association with colorectal adenoma among 1,711 participants in a cross-sectional study of colorectal adenoma. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) of colorectal adenoma using logistic regression models. Variances in hsCRP explained by body mass index were 61.1% in men and 64.5% in women in the prediction model. The increasing predicted hsCRP score was positively associated with colorectal adenoma (OR quartile 4 VS quartile 1 1.71, 95% CI: 1.12–2.62; \( P_{\text{trend}} = 0.011 \) in men; OR quartile 4 VS quartile 1 2.86, 95% CI: 1.26–6.49; \( P_{\text{trend}} = 0.019 \) in women). In subgroups, the associations differed by age and menopausal status among women, with stronger associations among women aged less than 50 years (OR ≥ median VS < median 3.74, 95% CI: 1.77–7.90, \( p \) for interaction 0.014) or premenopausal women (OR ≥ median vs < median 4.21, 95% CI: 2.12–8.36, \( p \) for interaction < 0.001). The associations were more pronounced in the advanced or distal colon/rectum in men and in the advanced or proximal colon in women. The associations were attenuated after further adjustment for body mass index. In conclusion, we found that the predicted hsCRP score was positively associated with colorectal adenoma, suggesting that diet and lifestyle lowering inflammation may be a strategy to prevent colorectal neoplasia.

Colorectal cancer has been the third most common cancer in men and the second in women worldwide¹. In Korea, colorectal cancer was the second most common cancer in men and the third in women². The World Cancer Research Fund (WCRF) reported that being physically active, consuming intakes of whole grains, foods containing dietary fiber and dairy products, and taking calcium supplements decreased the risk of colorectal cancer, while consuming red meat, processed meat and alcohol, and being overweight or obese and tall increased the risk³.

Chronic inflammation may play an important role in colorectal neoplasia, considering that chronic inflammation is thought to predispose individuals to cancer⁴. For example, chronic inflammatory conditions, including Crohn’s disease and chronic ulcerative colitis, were risk factors of colorectal carcinoma⁵, whereas nonsteroidal anti-inflammatory drug use reduced the risk of colorectal cancer⁶. Chronic inflammation has been hypothesized to stimulate tumor growth and progression by producing proinflammatory cytokines that activate the transcription factors of tumor cells⁴. Several studies reported that high circulating levels of C-reactive protein (CRP) were associated with risk of colorectal cancer⁷ and higher prevalence of colorectal adenoma⁸, a precancerous lesion of colorectal cancer.

Several studies reported that diet, age, body mass index (BMI), socioeconomic status, and physical activity were linked to inflammatory status⁹–¹⁶. Diet factors in relation to inflammation have been identified in a number of studies exploring a priori or a posteriori dietary patterns⁹–¹². Obesity was associated with elevated levels of CRP as adipocytes synthesize and secrete interleukin-6 (IL-6) and CRP¹³, whereas physical activity lowered levels of CRP¹⁴. Also, CRP levels differed by age, race, and gender¹⁵.

A Dietary Inflammatory IndexTM (DII®) has been recently developed based on the literature review of pro- or anti-inflammatory foods and nutrients¹⁶, and high scores of DII were positively associated with colorectal cancer

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risk\textsuperscript{17}. Also, an empirically derived dietary pattern that reflected pro-inflammatory status was associated with the risk of colorectal cancer\textsuperscript{18}.

In the current study, we developed an index that predicted levels of high-sensitivity C reactive protein (hsCRP), an indicator of chronic inflammation, from foods, nutrients, and lifestyle-related factors in more than 20,000 Korean adults. We further validated the predicted hsCRP score in an independent population, the colorectal adenoma study, and examined whether the predicted hsCRP scores were associated with colorectal adenoma in Korean men and women.

Material and Methods
Development of the predicted hsCRP score. Study population. We developed the predicted hsCRP score in participants of the Health Examinees (HEXA) Study in Korea, a large-scale genomic population-based study. The HEXA Study forms the largest subcohort of the Korean Genome and Epidemiology Study (KoGES), the principal purpose of which is to investigate epidemiologic characteristics and genomic risk factors for chronic diseases in the Korean population\textsuperscript{19}. Participants in the HEXA study were recruited at health examination centers and training hospitals in Korea. A total of 173,357 participants aged 40–79 years were enrolled in the HEXA Study from 2004 to 2013. Details of enrollment and data collection are described elsewhere\textsuperscript{20}. In this study, out of the 61,398 participants whose levels of hsCRP were measured with the same analyzer between January, 2004 and October, 2007 and we excluded participants whose hsCRP values were missing (n = 82), and whose hsCRP values were more than 10 mg/L, which is considered acute inflammatory status (n = 1,065)\textsuperscript{21}. And we further excluded participants who reported taking hypertension medicine or were diagnosed with hypertension, diabetes, hyperlipidemia, stroke, ischemia, myocardial infarction, or cancer at enrollment (n = 18,829). KoGES provided food frequency questionnaires (FFQs) data after excluding individuals: 1) who did not respond to any questions of FFQs, 2) who left more than 12 blanks for frequency questions, 3) who did not answer any questions about rice intake, or 4) who had extremely low (<100 kcal/day) or high (>10,000 kcal/day) energy intake, resulting in exclusion of 1,885 participants. And we further excluded participants who had implausible energy intake (<800 or >4,200 kcal per day for men, <500 or >3,500 kcal per day for women, n = 1,257). Because the disproportionality of sex in the dataset could influence the derivation of the predicted hsCRP score, we included the equal number of men and women by matching men and women by the exact age. As a result, a total of 23,330 participants (11,665 men and 11,665 women) from the HEXA Study were included. All participants provided written informed consent forms to participate in the study. The study was reviewed and approved by the Institutional Review Board of Seoul National University. All of the methods were performed in accordance with the relevant guidelines and regulations.

Assessment of the hsCRP levels, diet, and other variables. Blood samples were collected after an 8-hour overnight fast. After the sampling and labeling process, blood samples were centrifuged and stored at 4 °C until analysis. Serum hsCRP levels were measured on a Hitachi 7080 automatic analyzer (Hitachi, Japan) using latex immune complex turbidimetrics (Pure Auto S CRP latex, Daiichi, Japan). The intra-assay coefficient of variation (CV) was 1.63%.

Educated and trained interviewers used a standardized questionnaire survey complying with the study protocol to ask participants about sociodemographic characteristics, including educational level, income, and occupation, medical history, medication use, alcohol intake, smoking status, dietary habits, physical activities, and, for women, reproductive factors.

Participants completed the self-administered 106-item FFQs developed for the Korean population. The reliability of the FFQ has been examined by comparing the dietary intakes from the average amounts based on the first and second FFQ and its validity was examined by comparing 3 dietary records every season, 12-day dietary records (DRs) in total. Pearson correlation coefficients between the FFQ and the 12-day DRs adjusted for age, sex and energy intake were 0.64 for carbohydrate and 0.43 for protein and Pearson correlation coefficients between the first and second FFQs were 0.56 for fat and 0.49 for protein\textsuperscript{22}. Nine possible frequency responses, ranging from “not at all or less than once a month” to “three times per day” during the previous one year, were available for each food item. The portion size for each item was reported as one of three sizes: one-half of a standard serving and energy intake were 0.64 for carbohydrate and 0.43 for protein and Pearson correlation coefficients between the first and second FFQs were 0.56 for fat and 0.49 for protein\textsuperscript{22}. Nine possible frequency responses, ranging from “not at all or less than once a month” to “three times per day” during the previous one year, were available for each food item. The portion size for each item was reported as one of three sizes: one-half of a standard serving size, one serving size, or one and one-half serving size. Average daily intakes of foods and nutrients were calculated by multiplying the frequency of consumption by the reported amount. To take into account food groups that may be related to inflammation, we classified the 106 items on the FFQ into 38 food groups based on similarity of nutritional characteristics or preparation method (Supplementary Table 1).

We created the model that included thiamin, riboflavin, vitamin B-6, niacin, vitamin A, vitamin C, vitamin E, carbohydrate, total fat, monounsaturated fats, polyunsaturated fats, ω-3 fats, ω-6 fats, saturated fat, protein, fiber, iron, folate, caffeine, total cholesterol, flavanol, anthocyanidins, flavones, flavonols and isoflavones, which showed to be associated with inflammatory biomarkers\textsuperscript{15}. We calculated intakes of saturated fat, monounsaturated fatty acid, polyunsaturated fatty acid, ω-3 fats, ω-6 fats, caffeine, flavan-3-ol, flavones, flavonols, anthocyanidins, and isoflavones by referring to the databases of the Rural Development Administration (RDA), the Korea National Health and Nutrition Examination Survey (KNHANES) and the United States Department of Agriculture (USDA). Each nutrient was adjusted by energy intake using the residual method\textsuperscript{23}.

BMI was calculated by dividing the participant’s weight (kg) by the square of the height (m\textsuperscript{2}). Alcohol intake was estimated by summing up the ethanol weight after multiplying amounts and frequencies of specific types of liquors. Physical activities were estimated by multiplying the frequencies per week and times according to work-out types. For missing values of alcohol (0.05%) and BMI (1%), we assigned medians. For missing values of physical activity (3.10%), education level (2.47%) and smoking status (0.69%), participants were assigned to reference groups. If a woman's menopausal status was not reported (0.84%), we assumed that she was postmenopausal if she was 50 years or older.
Development of the predicted hsCRP score. The 38 food groups, nutrients, alcohol intakes, BMI, smoking status, physical activities, educational levels and menopausal status of women were initially included to derive the prediction model of hsCRP because these factors were associated with inflammation. We randomly divided the study population into a training set and 30% for a testing set. The training set was used to develop the score. The testing set was then used to evaluate the validity of the predicted hsCRP score by comparing the actual levels of hsCRP. The levels of hsCRP were log-transformed to improve the normality. We included the aforementioned variables as independent variables and log-transformed hsCRP as a dependent variable in a stepwise linear regression model in the training set, with \( p < 0.05 \) as the significance level for entry and retention. Also, we developed indices for men and women combined (sex-combined) and separately (men-specific and women-specific) and compared the potential inflammatory determinants by sex.

In the testing set, we computed predicted hsCRP scores by multiplying the individual’s response or estimated intake and the beta coefficient from the derived model. We calculated the least-square mean (LS-mean) for quartiles of the predicted hsCRP scores using the generalized linear model. We then calculated relative concentrations and 95% confidence intervals (CIs) as ratios of LS-mean levels of hsCRP among participants in each subsequent quartile of predicted hsCRP score to those among participants in the lowest quartile. We adjusted for sex (men, women), age (continuous, years), alcohol intake (0, 0-<15, 15-<30, ≥30 g/day for men, 0, 0-<5, 5-<10, ≥10 g/day for women), smoking status (past, current, never for men, never and ever for women), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above), and, in women only, menopausal status (premenopausal, perimenopausal, postmenopausal). We additionally adjusted for BMI (continuous, kg/m²) in a sensitivity analysis.

Association between the predicted hsCRP score and colorectal adenoma. Study population. Participants in the colorectal adenoma study were 1,056 men and 661 women who underwent colonoscopies for regular health check-ups at Seoul National University Hospital Gangnam Center between May and December 2011. We excluded participants who were diagnosed with colorectal cancer (n = 5); who had a medical history of colorectal cancer (n = 2); or whose energy intakes were implausible (<800 or >4,200 kcal per day for men, <500 or >3,500 kcal per day for women, n = 9). As a result, a total of 1,711 participants (1,056 men and 655 women) were included. We defined participants as having “advanced adenoma” if they had adenomas with villous component, with high-grade dysplasia, in sizes of more than 10 mm, or presence of three or more synchronous adenomas. Colorectal adenomas were divided into proximal colon, distal colon or rectum. The reference point between proximal and distal colon was splenic flexure. All participants provided written informed consent forms to participate in the study. The study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital.

Assessment of hsCRP levels, diet, and other variables. Participants were asked about sociodemographic characteristics, alcohol consumption, smoking status, educational levels, physical activities, family history of colorectal cancer, and menopausal status for women only. The participants reported time spent doing vigorous and mild exercise and walking. We calculated a metabolic equivalent task score (METs) for each physical activity. To estimate dietary intakes, participants were asked about the amounts and frequencies of consumption of each food item by a diettian using the same FFQs validated in KoGES. We directly measured height, weight and waist circumference and calculated BMI. Serum hsCRP was assessed using the ARCHITECT ci16200 (Abbott Laboratories, Abbott Park, IL, USA) automated immunoassay. The intra-assay CV was less than 2%. Participants underwent colonoscopy on the same day as the questionnaire surveys, anthropometric measures and blood draw. According to the colonoscopy findings, participants diagnosed with colorectal adenoma were cases and those without any adenoma were non-cases.

Statistical analysis. We computed the predicted hsCRP scores by multiplying individual’s response or estimated intake and the beta coefficient derived in a sex-specific way from the HEXA Study. We validated the sex-specific prediction model among a subset of non-cases with hsCRP values (n = 659) in the colorectal adenoma study by calculating the relative concentrations of hsCRP levels according to the predicted hsCRP scores. We calculated the LS-means for quartiles of predicted hsCRP scores using the generalized linear model. Then, we calculated relative concentrations and 95% confidence intervals (CIs) as ratios of LS-mean levels of hsCRP among participants in each subsequent quartile of predicted hsCRP score to those among participants in the lowest quartile. To examine the associations of actual hsCRP levels and predicted hsCRP scores with colorectal adenoma, we calculated ORs and 95% CIs using logistic regression models. We categorized study participants into quartiles according to the predicted hsCRP scores and actual hsCRP levels, respectively. The general characteristics from the colorectal adenoma study population were reported as the means with standard deviations among the continuous variables and as percentages among the categorical variables, according to quartiles of the predicted hsCRP score. In the multivariate model, we adjusted for age (continuous, year), alcohol intake (0, 0-<15, 15-<30, ≥30 g/day for men and 0, 0-<15, 15-<30, ≥30 g/day for women), smoking status (past, current, never for men and never and ever for women), physical activity (none, <14, ≥14 METs-hours per week), education levels (high school or less, university or above) and, in women only, menopausal status (premenopausal, perimenopausal, postmenopausal). We further adjusted for BMI (continuous, kg/m²), as obesity might induce inflammation and be an intermediate factor. The median values of each category were assigned and used as a continuous variable to test the linear trends. We tested for potential effect modifiers by including an interaction term of calculated score classified by median values of the predicted hsCRP score and age, waist circumference, and menopausal status. A likelihood ratio test was used to compare nested models that included cross-product terms with the original models that did not include terms.
| Sex-combined       | Beta  | p value | Men-specific       | Beta  | p value | Women-specific       | Beta  | p value |
|--------------------|-------|---------|--------------------|-------|---------|----------------------|-------|---------|
| Positively associated |      |         |                    |       |         |                      |       |         |
| Alcohol intake* (g/d) | 0.0009| 0.002   | Niacin (mg/d)      | 0.1360| 0.002   | Beef (g/d)            | 0.0009| 0.040   |
| Breakfast cereals/mixed grain powder (g/d) | 0.0015| 0.035   | Noodles/dumplings (g/d) | 0.0004| <0.001  | Processed fish (g/d) | 0.0028| 0.013   |
| Noodles/dumplings (g/d) | 0.0003| <0.001  | Age (y)            | 0.0113| <0.001  | Age (y)               | 0.0140| <0.001  |
| Potatoes (g/d) | 0.0012| 0.016   | BMI (1 kg/m²)      | 0.0707| <0.001  | BMI (1 kg/m²)         | 0.0782| <0.001  |
| Beef (g/d) | 0.0011| <0.001  | Smoking status     |       |          | Smoking status        |       |          |
| Carbonated beverages (g/d) | 0.0003| 0.018   | Never               |       |          | Reference             |       |          |
| Age (y) | 0.0158| <0.001  | Past smoker         | 0.0370| 0.081   | Past smoker            | 0.1514| 0.056   |
| BMI (1 kg/m²) | 0.0773| <0.001  | Current smoker      | 0.1990| <0.001  | Current smoker         | 0.1360| 0.016   |
| Smoking status |       |          | Smoking status      |       |          | Smoking status         |       |          |
| Never |       |          | Reference            |       |          | Reference              |       |          |
| Past smoker | 0.0787| <0.001  | Perimenopause       | 0.0587| 0.043   | Perimenopause          | 0.1576| <0.001  |
| Current smoker | 0.2547| <0.001  | Postmenopause       |       |          | Postmenopause          |       |          |
| Negatively associated |      |         |                     |       |         |                      |       |         |
| Soup and stew with soybean paste/soybean paste (g/d) | −0.0042| <0.001 | Soup and stew with soybean paste/soybean paste (g/d) | −0.0055| 0.002  | Soup and stew with soybean paste/soybean paste (g/d) | −0.0033| 0.031  |
| Sweet potatoes (g/d) | −0.0010| 0.007  | Sweet potatoes (g/d) | −0.0017| 0.017  | Sweet bread (g/d)     | −0.0010| 0.020  |
| Sweet bread (g/d) | −0.0007| 0.035  | Exercise            |       |          | Fish (g/d)            | −0.0007| 0.014  |
| Fruits (g/d) | −0.0001| 0.200  | None               |       |          | Reference              |       |          |
| Exercise |     |         | 0 < < 3.5 times/d | −0.1283| <0.001  | Elementary school or below |       | Reference |
| None |       |         | ≥3.5 times/d       | −0.1002| <0.001  | Middle school          | −0.0659| 0.010  |
| 0 < < 3.5 times/d | −0.0586| <0.001  | High school         | −0.0256| 0.271   | University or above    | 0.0247| 0.395   |
| ≥3.5 times/d | −0.0707| <0.001  |                   |       |          |                      |       |          |

Table 1. Components of the predicted hsCRP scores based on foods, nutrients and lifestyle factors in sex-combined and sex-specific model. *Alcohol intake was estimated by summing up the ethanol weight after multiplying amounts and frequencies of specific types of alcoholic beverages. The food group included the following food items: breakfast cereals/mixed grain powder, breakfast cereals and mixed grain powder; noodles/dumplings, noodles, instant noodles, noodles in blackbean sauce, spicy seafood noodle soup, cold noodles, dumplings, and japchae; soup and stew with soybean paste/soybean paste, soup and stew with soybean paste, soybean paste, and seasoning soybean paste; sweet bread, red bean bread, and doughnuts; fruits, tangerine, orange, strawberries, watermelon, apples, pear, bananas, and grapes; processed fish, canned tuna fish and fish cake.

We used polytomous logistic regression to conduct stratified analyses according to the progress and location of the colorectal adenoma. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA); all tests were two-sided, and P < 0.05 was considered statistically significant.

Results

Development of predicted hsCRP score. When we developed the predicted hsCRP model, the components of the prediction model based on the foods, nutrients, and lifestyle related variables differed between the sex-combined model and sex-specific models (Table 1). Age, BMI, and smoking status were selected in all three models (sex-combined, men-specific, and women-specific). Older age, higher BMI, and being a past or current smoker were associated with higher levels of hsCRP. Physical activity was included in the sex-combined and men-specific models, but not in the women-specific model and engagement in exercise was inversely associated with hsCRP levels. Education levels and menopausal status remained only in the women-specific model. Regarding dietary factors, higher levels of hsCRP were associated with: higher intakes of alcohol, breakfast cereals/mixed grain powder, noodles/dumplings, potatoes, beef, and carbonated beverages; and, lower intakes of sweet bread, soup and stew with soybean paste/soybean paste, sweet potatoes, and fruits in the sex-combined model. Dietary factors selected in the men-specific model were different from those in the women-specific model. Among men only, there were positive associations for intakes of niacin and noodles/dumplings and inverse associations for intakes of sweet potatoes and soup and stew with soybean paste/soybean paste. In the women-specific model, increasing intakes of beef and processed fish and decreasing intakes of fish, soup and stew with soybean paste/soybean paste and sweet bread, sweet red bean bread, and doughnuts; fruits, tangerine, orange, strawberries, watermelon, apples, pear, bananas, and grapes; processed fish, canned tuna fish and fish cake.

We found that the relative concentrations of the actual levels of hsCRP in the testing set increased according to increasing quartiles of the predicted hsCRP score (Table 2). In the sex-combined model, the relative concentrations (95% CIs) for the highest compared with the lowest predicted hsCRP score were 1.82 (95% CI: 1.66–2.00) for men and women combined, 1.64 (95% CI: 1.46–1.83) among men and 1.90 (95% CI: 1.65–2.19) among
| Sex-combined model (n = 7,108) | Quartiles of the predicted hsCRP score | p for trend |
|--------------------------------|--------------------------------------|------------|
|                               | Quartile 1  | Quartile 2  | Quartile 3  | Quartile 4  |
| Unadjusted model              | Reference   | 1.00 ± 1.16 | 1.00 ± 1.16 | 1.00 ± 1.16 |
| Age-adjusted model            | Reference   | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.16) | 1.11 (1.05, 1.17) | 0.001 |
| Multivariate adjusted model   | Reference   | 1.05 (0.99, 1.12) | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.17) | 0.001 |

| Men in sex-combined model (n = 3,554) | Quartiles of the predicted hsCRP score | p for trend |
|-------------------------------------|--------------------------------------|------------|
|                                     | Quartile 1  | Quartile 2  | Quartile 3  | Quartile 4  |
| Unadjusted model                    | Reference   | 1.00 ± 1.16 | 1.00 ± 1.16 | 1.00 ± 1.16 |
| Age-adjusted model                  | Reference   | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.16) | 1.11 (1.05, 1.17) | 0.001 |
| Multivariate adjusted model         | Reference   | 1.05 (0.99, 1.12) | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.17) | 0.001 |

| Women in sex-combined model (n = 3,554) | Quartiles of the predicted hsCRP score | p for trend |
|---------------------------------------|--------------------------------------|------------|
|                                      | Quartile 1  | Quartile 2  | Quartile 3  | Quartile 4  |
| Unadjusted model                      | Reference   | 1.00 ± 1.16 | 1.00 ± 1.16 | 1.00 ± 1.16 |
| Age-adjusted model                    | Reference   | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.16) | 1.11 (1.05, 1.17) | 0.001 |
| Multivariate adjusted model           | Reference   | 1.05 (0.99, 1.12) | 1.07 (1.01, 1.15) | 1.09 (1.03, 1.17) | 0.001 |

| Men-specific model (n = 3,560) | Quartiles of the predicted hsCRP score | p for trend |
|--------------------------------|--------------------------------------|------------|
|                               | Quartile 1  | Quartile 2  | Quartile 3  | Quartile 4  |
| Unadjusted model              | Reference   | 1.00 ± 1.16 | 1.00 ± 1.16 | 1.00 ± 1.16 |
| Age-adjusted model            | Reference   | 1.06 (1.01, 1.14) | 1.08 (1.03, 1.16) | 1.10 (1.05, 1.17) | 0.001 |
| Multivariate adjusted model   | Reference   | 1.04 (0.99, 1.10) | 1.07 (1.02, 1.15) | 1.09 (1.04, 1.17) | 0.001 |

| Women-specific model (n = 3,560) | Quartiles of the predicted hsCRP score | p for trend |
|---------------------------------|--------------------------------------|------------|
|                                 | Quartile 1  | Quartile 2  | Quartile 3  | Quartile 4  |
| Unadjusted model                | Reference   | 1.00 ± 1.16 | 1.00 ± 1.16 | 1.00 ± 1.16 |
| Age-adjusted model              | Reference   | 1.06 (1.01, 1.14) | 1.08 (1.03, 1.16) | 1.10 (1.05, 1.17) | 0.001 |
| Multivariate adjusted model     | Reference   | 1.04 (0.99, 1.10) | 1.07 (1.02, 1.15) | 1.09 (1.04, 1.17) | 0.001 |

Table 2. Relative concentrations and 95% confidence intervals between the predicted hsCRP scores and the actual hsCRP levels in the testing set of the HEXA. *Adjusted for sex (men, women), age (continuous, years), alcohol (0, 0 < 15, 15 ≤ 30, ≥ 30 g/d), smoking status (past, current, never), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above). 1Adjusted for sex (men, women), age (continuous, years), alcohol (0, 0 < 15, 15 ≤ 30, ≥ 30 g/d), smoking status (past, current, never), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above), and BMI (continuous, kg/m²). 2Adjusted for age (continuous, years), alcohol (0, 0 < 15, 15 ≤ 30, ≥ 30 g/d), smoking status (past, current, never), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above), and BMI (continuous, kg/m²). 3Adjusted for age (continuous, years), alcohol (0, 0 < 15, 15 ≤ 30, ≥ 30 g/d), smoking status (past, current, never), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above), and menopausal status (postmenopausal, perimenopausal, postmenopausal). 4Adjusted for age (continuous, years), alcohol (0, 0 < 5, 5 ≤ 10, ≥ 10 g/d), smoking status (ever, never), regular physical exercise (none, <3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above), and BMI (continuous, kg/m²). When we estimated the relative concentrations using the men-specific and women-specific models, the relative concentrations comparing participants with the highest predicted hsCRP score and the lowest predicted hsCRP score were 1.65 (95% CI: 1.49–1.84) among men and 2.02 (95% CI: 1.74–2.34) among women. When we further adjusted for BMI, the relative concentrations of the highest predicted hsCRP score were 1.17 (95% CI: 0.98–1.40) among men and 1.14 (95% CI: 0.93–1.41) among women in sex-specific models.

**Association between predicted hsCRP score and colorectal adenoma.** The general characteristics of men and women by quartiles of the predicted hsCRP scores are presented in Table 3. Men who had the higher predicted hsCRP score were more likely to be older, current smokers and to have higher BMI. Men in the 3rd or 4th quartiles had lower proportions of university or above education and 14 or greater METs-hours per week of exercise compared to those in the 1st or 2nd quartiles. Women who had the higher predicted hsCRP scores tended to be older, postmenopausal and to have higher BMI and lower proportions of university or above education compared to those with lower scores.
When we estimated the relative concentrations of actual hsCRP levels in the colorectal adenoma study, the relative concentrations comparing participants with the highest predicted hsCRP score and the lowest predicted hsCRP score were 2.13 (95% CI: 1.43–3.17; $P_{\text{for trend}}<0.001$) among men and 2.82 (95% CI: 1.58–5.03; $P_{\text{for trend}}<0.001$) among women (Table 4). When we additionally adjust for BMI, trend became non-significant.

When we examined the association between actual hsCRP levels and colorectal adenoma, we found that increasing levels of actual hsCRP were associated with increasing prevalence of colorectal adenoma in men ($P_{\text{for trend}}=0.020$) and women ($P_{\text{for trend}}=0.003$) (Supplementary Table 2).

We found that increasing predicted hsCRP scores were associated with increasing prevalence of colorectal adenoma (Table 5). Compared with participants in the lowest quartile, the ORs of colorectal adenoma among

| Quartiles of the predicted hsCRP score | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---------------------------------------|------------|------------|------------|------------|
| Men (n = 1,056)                       | (n = 264)  | (n = 264)  | (n = 264)  | (n = 264)  |
| Number of cases/non-cases             | 75/189     | 98/166     | 110/154    | 123/141    |
| Age (years, %)                        | 47.9 ± 8.0 | 51.4 ± 8.4 | 52.6 ± 8.1 | 54.5 ± 9.4 |
| < 50 years                            | 141 (53.4) | 107 (40.5) | 98 (37.1)  | 73 (27.7)  |
| ≥ 50 years                            | 123 (46.6) | 157 (59.5) | 166 (62.9) | 191 (72.4) |
| Smoking status (%)                    |            |            |            |            |
| Never                                 | 103 (39.5) | 67 (25.8)  | 57 (22.1)  | 35 (13.4)  |
| Past smoker                           | 123 (47.1) | 137 (52.7) | 107 (41.5) | 97 (37.2)  |
| Current smoker                        | 35 (13.4)  | 56 (21.5)  | 94 (36.4)  | 129 (49.4) |
| BMI (kg/m²)                           | 21.9 ± 1.8 | 23.8 ± 1.4 | 25.1 ± 1.6 | 27.2 ± 2.0 |
| Educational level (%)                 |            |            |            |            |
| High school or less                   | 22 (8.0)   | 37 (14.5)  | 40 (16.1)  | 46 (18.2)  |
| University or above                   | 233 (91.4) | 219 (85.5) | 209 (83.9) | 207 (81.8) |
| Alcohol intake (%)                    |            |            |            |            |
| 0 g                                   | 22 (8.5)   | 25 (9.7)   | 32 (12.7)  | 30 (11.8)  |
| 0 g < 15 g                            | 109 (42.1) | 87 (33.7)  | 66 (26.1)  | 74 (29.0)  |
| 15 g ≤ 30 g                           | 55 (21.2)  | 59 (22.9)  | 64 (25.3)  | 50 (19.6)  |
| Exercise (%)                          |            |            |            |            |
| None                                  | 62 (23.9)  | 87 (33.5)  | 114 (44.7) | 127 (49.0) |
| 0 < 14 METs-hours/week                | 81 (31.2)  | 58 (22.3)  | 44 (17.3)  | 29 (11.2)  |
| ≥ 14 METs-hours/week                  | 117 (45.0) | 115 (44.2) | 97 (38.0)  | 103 (39.8) |
| Women (n = 655)                       | (n = 163)  | (n = 164)  | (n = 164)  | (n = 164)  |
| Number of cases/non-cases             | 14/149     | 31/133     | 48/116     | 56/108     |
| Age (years, %)                        | 41.8 ± 5.4 | 47.8 ± 6.0 | 53.4 ± 6.7 | 58.1 ± 7.8 |
| < 50 years                            | 146 (89.6) | 100 (61.0) | 40 (24.4)  | 19 (12.0)  |
| ≥ 50 years                            | 17 (10.4)  | 64 (39.0)  | 124 (75.6) | 145 (88.4) |
| Smoking status (%)                    |            |            |            |            |
| Never                                 | 149 (92.6) | 145 (90.1) | 154 (95.7) | 142 (87.7) |
| Past smoker                           | 5 (3.1)    | 11 (6.8)   | 4 (2.5)    | 11 (6.8)   |
| Current smoker                        | 7 (4.4)    | 3 (1.9)    | 3 (1.9)    | 9 (5.6)    |
| BMI (kg/m²)                           | 19.4 ± 1.3 | 21.2 ± 1.6 | 22.3 ± 1.8 | 25.3 ± 3.1 |
| Post-menopausal status (%)            | 8 (5.1)    | 51 (31.9)  | 108 (67.5) | 136 (84.0) |
| Educational level (%)                 |            |            |            |            |
| High school or less                   | 26 (16.7)  | 37 (24.2)  | 48 (31.6)  | 61 (39.9)  |
| University or above                   | 130 (83.3) | 116 (75.8) | 104 (68.4) | 92 (60.1)  |
| Alcohol intake (%)                    |            |            |            |            |
| 0 g                                   | 66 (42.3)  | 67 (42.4)  | 73 (46.5)  | 93 (60.0)  |
| 0 g < 15 g                            | 77 (49.4)  | 70 (44.3)  | 73 (45.2)  | 47 (30.3)  |
| 15 g ≤ 30 g                           | 7 (4.5)    | 9 (5.7)    | 8 (5.1)    | 10 (6.5)   |
| Exercise (%)                          |            |            |            |            |
| None                                  | 74 (46.5)  | 73 (45.9)  | 79 (50.0)  | 80 (50.0)  |
| 0 < 14 METs-hours/week                | 36 (22.6)  | 26 (16.4)  | 30 (19.0)  | 30 (18.8)  |
| ≥ 14 METs-hours/week                  | 49 (30.8)  | 60 (37.7)  | 49 (31.0)  | 50 (31.3)  |

**Table 3.** Characteristics by quartiles of the predicted hsCRP score using sex-specific models among men and women in the colorectal adenoma study. Data are expressed as arithmetic mean ± SD if not stated otherwise.
those in the highest quartile of the predicted hsCRP score were 1.71 (95% CI: 1.12–2.62; P for trend = 0.011) among men and 2.86 (95% CI: 1.26–6.49; P for trend = 0.019) among women. When we further adjusted for BMI, the ORs comparing the highest quartiles with the lowest quartiles of the predicted hsCRP score were attenuated to 0.98 (95% CI: 0.42–2.31) in men and 1.61 (95% CI: 0.46–5.64) in women.

We examined whether the associations between the predicted hsCRP scores and colorectal adenoma were modified by age, waist circumference and menopausal status (Table 6). Significant differences were not observed when stratified by waist circumference in either men or women. The interactions by age and menopausal status were significant among women. When we stratified women by age (<50 or ≥50 years), the ORs (95% CIs) comparing equal to and more than median values of predicted hsCRP score with under the median values were 3.74 (95% CI: 1.77–7.90) for women who were under 50 years and 1.09 (95% CI: 0.57–2.07) for women who were 50 years or older (p for interaction = 0.014). The ORs for comparing equal to and more than median values of predicted hsCRP score with under the median values were 4.21 (95% CI: 2.12–8.36) for premenopausal women and 0.71 (95% CI: 0.36–1.41) for postmenopausal women (p for interaction <0.001).

We further examined the association between the predicted hsCRP score and colorectal adenoma according to progressive stage and location (Table 7). Stronger associations between the predicted hsCRP scores and advanced adenoma were observed in both men (OR: 1.62, 95% CI: 1.00–2.63) and women (OR: 6.55, 95% CI: 1.62–26.37). When we additionally adjusted for BMI, ORs (95% CIs) were 1.30 (95% CI: 0.67–2.52) among men and 3.51 (95% CI: 0.75–16.40) among women. When stratified by anatomical sites among men, the association was statistically significant for distal colon and rectal adenomas (OR: 1.83, 95% CI: 1.21–2.77), but not for proximal colon adenomas. Whereas among women, the association was stronger for proximal colon adenoma than for distal colon and rectal adenomas. Women with median or higher values of the predicted hsCRP scores had a 1.95 times higher prevalence of proximal colon adenoma compared to those with lower than median values.

### Discussion

In this cross-sectional study, we derived the predicted score to reflect chronic inflammatory status. We found that the predicted hsCRP scores were correlated with actual hsCRP levels in the colorectal adenoma study participants, suggesting that the predicted hsCRP scores may reflect inflammatory status in Korean adult populations. We found that men and women with high predicted hsCRP scores had higher prevalence of colorectal adenoma compared to those with low scores. The associations were more pronounced among women aged less than 50 years or premenopausal. Men and women with high predicted hsCRP scores had higher prevalence of advanced colorectal adenoma compared to those with low predicted scores, but this association was not observed for non-advanced adenoma.

We found that the higher intakes of noodles/dumplings, beef, breakfast cereals/mixed grain powder, potatoes, carbonated beverages, and processed fish and the lower intakes of soybean paste/soup and stew with soybean paste, sweet potatoes, sweet breads, fruits, and fish were associated with increased levels of hsCRP. Our findings for dietary factors related to inflammation corroborate the results of other previous studies. In the empirically derived inflammatory pattern of the Nurses’ Health Study, higher intakes of processed meat, red meat, organ meat, refined grains and high-energy beverages and lower intakes of dark yellow vegetables including sweet potatoes, snacks, and

### Table 4.

Relative concentrations and 95% CIs between the predicted hsCRP scores of sex-specific models and actual hsCRP levels among non-case participants in the colorectal adenoma study. aAdjusted for age (continuous, years), alcohol (0, 0–<15, 15–<30, ≥30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), and educational level (high school or below, university or above). bAdjusted for age (continuous, years), alcohol (0, 0–<15, 15–<30, ≥30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and BMI (continuous, kg/m²). cAdjusted for age (continuous, years), alcohol (0, 0–<15, 15–<30, ≥30 g/d), smoking status (ever, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal). dAdjusted for age (continuous, years), alcohol (0, 0–<15, ≥15 g/d), smoking status (ever, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal), and BMI (continuous, kg/m²).

| Quartiles of the predicted hsCRP score | p for trend |
|---------------------------------------|------------|
| Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
| **Men (n = 352)**                      |            |            |            |
| hsCRP, mg/L, mean ± SD                |            |            |            |
| Age-adjusted model                    | 0.24 ± 0.07| 0.49 ± 0.08| 0.90 ± 0.17| 2.71 ± 1.67|
| Multivariate adjusted model           | 1.42 (1.01, 2.01) | 1.61 (1.12, 2.32) | 1.96 (1.35, 2.86) | < 0.001 |
| Multivariate adjusted model           | 1.46 (1.01, 2.09) | 1.77 (1.20, 2.59) | 2.13 (1.43, 3.17) | < 0.001 |
| Multivariate adjusted model           | 1.04 (0.65, 1.66) | 1.05 (0.63, 1.75) | 0.94 (0.50, 1.79) | 0.859 |
| **Women (n = 293)**                   |            |            |            |
| hsCRP, mg/L, mean ± SD                |            |            |            |
| Age-adjusted model                    | 0.17 ± 0.05| 0.38 ± 0.08| 0.81 ± 0.18| 2.54 ± 1.68|
| Multivariate adjusted model           | 1.47 (0.92, 2.34) | 1.56 (0.98, 2.48) | 2.45 (1.45, 4.13) | < 0.001 |
| Multivariate adjusted model           | 1.54 (0.92, 2.59) | 1.71 (1.02, 2.85) | 2.82 (1.58, 5.03) | < 0.001 |
| Multivariate adjusted model           | 1.19 (0.62, 2.29) | 1.11 (0.57, 2.15) | 1.38 (0.57, 3.33) | 0.554 |
The Nurses' Health Study reported that the hazard ratios (HRs) of the highest quintile of empirical dietary pattern and risk of colorectal cancer\(^{38}\). In that study, high scores of the CRP-dietary pattern scores were positively associated with the intakes of grains, salted fermented seafood, carbonated beverages, seafood/seashell, oils, noodles, and sweets. In contrast, the intakes of fruits, bonafish, vegetables, milk, nuts, tubers, tea/beverages, seaweeds, and condiments/seasonings were inversely associated with the dietary pattern scores.

When we compared the sex-combined and sex-specific models, we observed that the components of the prediction models and the magnitude of the relative concentrations differed by sex. Although differences of CRP by sex were controversial, it was reported that levels of hsCRP in women were higher than men in the U.S. population\(^{16,25}\). In contrast, men had higher CRP levels than both pre- and postmenopausal women in Japanese\(^{40}\) and Korean population\(^{28}\). It is well-known that men and women have different physical and physiological characteristics, for example, body composition and sex hormones\(^{41}\). In vivo and in vitro studies found that endogenous sex steroids might act as inflammatory regulators in the inflammatory processes\(^{12}\). Sex differences in components related to hsCRP levels might be partly explained by biological difference. Also, sex difference that we found could be due to differences in dietary intake\(^{39,44}\). A previous Korean study found sex differences in the amount of food and selection of food items in the KNHNAES\(^{28}\).

We observed that higher values of the actual hsCRP and predicted hsCRP scores were associated with higher prevalence of the colorectal adenoma in both men and women. However, further adjustment for BMI attenuated the associations between hsCRP levels and colorectal adenoma. The reason why we found the attenuation after further adjustment for BMI might be because BMI was a strong determinant for hsCRP levels.

Chronic inflammation contributes to development and progression of cancer\(^{45}\). Chronic inflammation activates the transcription factors such as NF-κB and signal transducer and activator of transcription 3 (STAT3) of tumor cells\(^{46}\). These activated transcription factors stimulate production of cytokines and chemokines, resulting in recruitment of various leukocytes\(^{4}\). This leads to cell proliferation, angiogenesis and lymphangiogenesis and invasion of tumor cells\(^{48}\). A recent meta-analysis has revealed that elevated CRP levels were associated with colorectal cancer\(^{2}\) and colorectal advanced adenoma\(^{46}\). The DIIT\(^{12}\) was developed based on the literature review\(^{12}\) and was found to be positively associated with prevalence of colorectal adenoma\(^{37}\) and the risk of colorectal cancer\(^{46}\). The Nurses' Health Study reported that the hazard ratios (HRs) of the highest quintile of empirical dietary inflammatory pattern scores compared to the lowest were 1.44(95% CI: 1.19–1.74; \(P\) for trend < 0.001) among men and 1.22 (95% CI: 1.02–1.45; \(P\) for trend = 0.007) among women\(^{18}\).

In the prediction models, BMI, age, and smoking status were selected as determinants for hsCRP levels in both men and women. Obesity is associated with chronic inflammation\(^{45}\). Adipocytes produce inflammation-related factors such as IL-6, TNF-α, and adiponectin\(^{48}\). The overexpression of pro-inflammatory cytokines and IL-6 stimulates hepatocytes and drives the systemic inflammation in the body\(^{49}\). Oxidative stress produced from the cigarette burning and the aging process induces chronic upregulation of pro-inflammatory mediators activating the NF-κB signaling pathway\(^{49,51}\). These inflammatory mediators recruit chronic immune cells and promote inflammation\(^{49,51}\).

| Table 5. Odds ratio (ORs) and 95% confidence interval (CIs) for colorectal adenoma according to quartiles of the predicted hsCRP score of men-specific and women-specific models. \(^{a}\)Adjusted for age (continuous, years), alcohol (0, 0–15, 15–30, >30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), and educational level (high school or below, university or above). \(^{b}\)Adjusted for age (continuous, years), alcohol (0, 0–15, 15–30, >30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and BMI (continuous, kg/m\(^2\)). \(^{c}\)Adjusted for age (continuous, years), alcohol (0, 0–15, ≥15 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal). \(^{d}\)Adjusted for age (continuous, years), alcohol (0, 0–15, ≥15 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and BMI (continuous, kg/m\(^2\)). |
| --- |
| **Men (n = 1,056)** | **Quartiles of the predicted hsCRP score** | **Number of case/noncase** | **Age-adjusted model** | **Multivariate adjusted model\(^{a}\)** | **Multivariate adjusted model\(^{b}\)** | **Multivariate adjusted model\(^{c}\)** | **Multivariate adjusted model\(^{d}\)** | **p for trend** |
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | Reference | 1.27 (0.87, 1.85) | 1.46 (1.00, 2.12) | 1.63 (1.12, 2.38) | 0.009 | Reference | 1.30 (0.89, 1.91) | 1.52 (1.02, 2.27) | 1.71 (1.12, 2.62) | 0.011 | Reference | 1.06 (0.66, 1.70) | 1.08 (0.59, 1.98) | 0.98 (0.42, 2.31) | 0.974 |
| Number of case/noncase | 75/189 | 98/166 | 110/154 | 123/141 | | | | | | | | | | | | | | **Women (n = 655)** | **Quartiles of the predicted hsCRP score** | **Number of case/noncase** | **Age-adjusted model** | **Multivariate adjusted model\(^{a}\)** | **Multivariate adjusted model\(^{b}\)** | **Multivariate adjusted model\(^{c}\)** | **Multivariate adjusted model\(^{d}\)** | **p for trend** |
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | Reference | 2.03 (1.01, 4.06) | 2.97 (1.44, 6.10) | 3.15 (1.44, 6.91) | 0.007 | Reference | 1.88 (0.93, 3.81) | 2.87 (1.36, 6.03) | 2.86 (1.26, 6.49) | 0.019 | Reference | 1.57 (0.73, 3.37) | 2.07 (0.83, 5.16) | 1.61 (0.46, 5.64) | 0.512 |
| Number of case/noncase | 24/139 | 30/124 | 37/127 | 28/106 | | | | | | | | | | | | | |
In our study, physical activity in men-specific models and education level and menopausal status in women-specific models were included. Physical activity was significantly inversely associated with CRP in British men52. Regular exercise reduced toll-like receptor 4 (TLR4) expression and lowered lipopolysaccharide-stimulated IL-6 production53. Additionally, participants whose educational levels were college or above had lower CRP levels compared to those whose educational levels were high school or below26. The Women’s Health Study has reported that increasing predicted CRP scores were associated with increasing risk of colon, proximal, and distal cancers18. Inverse association between CRP levels and proximal colon, but positive association for distal colon adenoma in the CLUE II cohort study62. A Japanese case-control study found that the associations for CRP levels were only associated with increasing proximal colon, not with distal colon and rectum63. The Women’s Health Initiative Study reported that increase in colon cancer risk with increasing levels of DII was limited to men58. Our study had several strengths. The inflammatory prediction model was derived from more than 20,000 healthy participants. We validated the predicted hsCRP score both in the testing set and in the independent population with actual hsCRP levels. This study included more than 1,700 Korean participants who underwent colonoscopies, which enabled us to examine the entire colon. Our study also had some limitations. First, because

### Table 6. Odds ratio (OR)s and 95% confidence interval (CI)s according to the predicted hsCRP, stratified by risk factors.

| Age | No. cases/non-cases | OR (95% CI) | P for interaction |
|---|---|---|---|
| <52 years, median | 79/221 | 1.41 (0.91, 2.20) | 0.801 |
| ≥52 years | 94/134 | 1.42 (0.97, 2.10) | |
| <90 cm | 151/309 | 1.10 (0.72, 1.70) | 0.208 |
| ≥90 cm | 21/41 | 1.19 (0.63, 2.26) | |
| <80 cm | 34/212 | 0.89 (0.39, 2.02) | 0.651 |
| ≥80 cm | 10/67 | 3.17 (1.40, 7.18) | 0.014 |
| pre-menopause | 26/232 | 4.21 (2.12, 8.36) | <0.001 |
| post-menopause | 18/41 | 0.71 (0.36, 1.41) | |

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**Dichotomous category of the predicted hsCRP scores**

| <median | OR (95% CI) | ≥median |
|---|---|---|
| No. cases/non-cases | OR (95% CI) | No. cases/non-cases |
| 173/355 | 2.33 (1.36, 4.00) | 233/295 |
| 151/309 | 1.10 (0.72, 1.70) | 21/41 |
| 34/212 | 0.89 (0.39, 2.02) | 10/67 |
| 26/232 | 4.21 (2.12, 8.36) | 18/41 |
| 94/134 | 1.42 (0.97, 2.10) | |
| 21/41 | 1.19 (0.63, 2.26) | |
| 10/67 | 3.17 (1.40, 7.18) | |
| 26/52 | 4.21 (2.12, 8.36) | <0.001 |
| 74/170 | 0.71 (0.36, 1.41) | |

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**Men**

**Women**

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**Menopausal status**

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**Waist circumference**
this was a cross-sectional study, our study did not infer a clear temporal relationship. However, it is possible that habitual diet and lifestyle of individuals that we observed might not be modified by outcome because colorectal adenoma is asymptomatic. Second, a single measurement of hsCRP may not reflect participants’ long-period status. Also, we cannot rule out the presence of unmeasured or residual confounding factors or measurement error inherent in dietary assessments may exist.

In conclusion, we developed the predicted hsCRP score and found that increasing levels of predicted hsCRP were associated with increasing prevalence of colorectal adenoma in both men and women. Further adjustment for BMI attenuated the association, partly because predicted hsCRP scores was largely explained by adiposity. The associations were more pronounced for advanced adenoma and the magnitudes of associations were modified by age or menopausal status among women. Our study suggests the evidence that diet and lifestyle lowering chronic inflammation may be an important strategy to reduce the burden of colorectal neoplasia.

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Table 7. Odds ratio (ORs) and 95% confidence interval (CI)s according to the predicted hsCRP score, stratified by progression and location. aAdjusted for age (continuous, years), alcohol (0, 0–15, 15–<30, ≥30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), and educational level (high school or below, university or above). bAdjusted for age (continuous, years), alcohol (0, 0–15, 15–<30 g/d), smoking status (past, current, never), regular physical exercise (none, <14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal).

| Category                        | Men (n = 1,056) | Women (n = 655) |
|---------------------------------|-----------------|-----------------|
|                                 | No. cases/non-cases | OR (95% CI)    | No. cases/non-cases | OR (95% CI)    |
| All colorectal adenoma          |                 |                 |                    |                 |
| < median                        | 173/355         | Reference       | 45/282             | Reference       |
| ≥ median                        | 233/295         | 1.44 (1.10, 1.89) | 104/224            | 1.86 (1.13, 3.06) |
| Non-advanced adenoma            |                 |                 |                    |                 |
| < median                        | 137/355         | Reference       | 42/282             | Reference       |
| ≥ median                        | 155/295         | 1.30 (0.95, 1.79) | 80/224             | 1.49 (0.87, 2.55) |
| Advanced adenoma                |                 |                 |                    |                 |
| < median                        | 36/355          | Reference       | 3/282              | Reference       |
| ≥ median                        | 78/295          | 1.62 (1.00, 2.63) | 24/224             | 6.55 (1.62, 26.37) |
| Proximal colon                  |                 |                 |                    |                 |
| < median                        | 121/355         | Reference       | 23/282             | Reference       |
| ≥ median                        | 131/295         | 1.16 (0.83, 1.62) | 62/224             | 1.95 (1.02, 3.75) |
| Distal colon and rectum         |                 |                 |                    |                 |
| < median                        | 52/355          | Reference       | 22/282             | Reference       |
| ≥ median                        | 102/295         | 1.83 (1.21, 2.77) | 42/224             | 1.65 (0.82, 3.33) |

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### Author contributions

Jung Eun Lee and Sun Young Yang designed the study; Jung Eun Lee, Sun Young Yang and Young Sun Kim contributed to data collection; Sejin Kim and Jung Eun Lee drafted the first manuscript; Sejin Kim, Sihan Song and Jung Eun Lee contributed to statistical analysis; and all authors contributed to interpretation of the data and approved the final version of the manuscript.

### Competing interests

The authors declare no competing interests.

### Additional information

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