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Development of high sensitivity C-reactive protein score and its association with colorectal adenoma

고감도C반응단백 예측모델 개발 및 대장선종과의 연관성

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Abstract

Development of high sensitivity C-reactive protein score and its association with colorectal adenoma

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Chronic inflammation has been suggested to stimulate tumor growth and progression. A meta-analysis study reported that high levels of C-reactive protein (CRP) were associated with higher prevalence of colorectal adenoma, a precancerous lesion of the colorectal cancer. We aimed to develop models that predicted levels of high-sensitivity C reactive protein (hsCRP), an indicator of chronic inflammation, in the Korean population. We developed the predicted hsCRP scores in the Health Examinees (HEXA) Study and examined the association between the predicted hsCRP score and colorectal adenoma in the separate population, colorectal adenoma study. The study participants (11,665 men and 11,665 women) of the HEXA study were randomly divided into two sets: 70% of the population was used as a training

set to develop the predicted hsCRP score and 30% of the population was used as a testing set. We included hsCRP as a dependent variable and foods, nutrients, and other lifestyle factors as independent variables in stepwise regression to derive the prediction model. We developed 4 versions of models that predicted hsCRP levels: 1) foods only; 2) foods and nutrients; 3) foods and other lifestyles, and 4) foods, nutrients and other lifestyles. The testing set was used to evaluate the validity of the predicted hsCRP score. Generalized linear model was used to calculate the relative concentration of actual hsCRP levels. Also we developed the predicted hsCRP score in men and women separately or combined and compared the components and validities of indices, as CRP levels and factors associated with CRP levels may differ by sex. Then we examined the association between the predicted hsCRP score and colorectal adenoma in the colorectal adenoma study (1,056 men and 655 women). Logistic regression was used to estimate odd ratios (ORs) and 95% confidence intervals (CIs). We found that the predicted hsCRP score was correlated with actual hsCRP levels in both men and women. The relative concentrations of hsCRP levels comparing extreme quartiles of predicted hsCRP score from sex-specific models in the HEXA study were: 1.65 (95% CI: 1.49, 1.84; p for trend <0.001) among men and 2.02 (95% CI: 1.74, 2.34; p for trend <0.001) among women. We found that increasing levels of actual hsCRP and predicted hsCRP score were associated with higher prevalence of colorectal adenoma in both men and women. The ORs of colorectal adenoma among participants in the highest quartile of the predicted hsCRP score compared with the lowest 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. In analyses stratified by potential effect modifiers, the associations were more pronounced among women aged less than 50 years than those aged 50 or greater years; the ORs of colorectal adenoma for comparing equal to and more than median values of the predicted hsCRP score with under the median values were: 3.74 (95% CI: 1.77, 7.90) for women who were under 50 years old and 1.09 (95% CI: 0.57, 2.07) for women who were 50 years or older (p for interaction = 0.014). Significant association between the predicted hsCRP scores and colorectal adenoma were observed only among women with high education levels or premenopausal women. The positive associations were limited to the distal colon/rectum in men, to the proximal colon in women and to the advanced colorectal adenoma in both men (OR: 1.62, 95% CI: 1.00, 2.63) and women (OR: 6.55, 95% CI: 1.62, 26.37). Our study suggests the evidence that diet and lifestyle lowering chronic inflammation may be an important strategy to reduce the burden of colorectal neoplasia.

Keyword: inflammation, high sensitivity C-reactive protein (hsCRP), prediction model, predicted hsCRP score, colorectal adenoma

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List of Abbreviations

BMI	Body mass index
CIs	Confidence intervals
CRP	C-reactive protein
DII	Dietary inflammatory index
EDIP	Empirical dietary inflammatory pattern
FFQ	Food frequency questionnaire
HEXA	Health examinees
HPFS	Health professionals follow-up study
HRs	Hazard ratios
hsCRP	high sensitivity C-reactive protein
KNHANES	Korea national health and nutrition examination survey
KoGES	Korean genome and epidemiology study
NHS	Nurses' health study
ORs	Odds ratios
RDA	Rural development administration
TNF-α	tumor necrosis factor-alpha
WCRF	World cancer research fund

I. Introduction

Colorectal cancer has been the third most common cancer in men and the second in women worldwide (Bray et al. 2018). In Korea, age-standardized incidence rates for colorectal cancer was the second in men and the third in women (Jung et al. 2018). 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 risk ((WCRF/AICR) 2018).

Chronic inflammation is thought to predispose individuals to cancer. Chronic inflammation may play an important role in colorectal neoplasia (Coussens and Werb 2002). For example, chronic inflammatory conditions, including Crohn's disease and chronic ulcerative colitis, risk factors for the development of colorectal carcinoma (Ullman and Itzkowitz 2011). Conversely, it was widely accepted that nonsteroidal anti-inflammatory drug use reduced the risk of colorectal cancer (González-Pérez, García Rodríguez, and López-Ridaura 2003). Chronic inflammation has been hypothesized to stimulate tumor growth and progression by producing proinflammatory cytokines that activate the transcription factors of tumor cells (Coussens and Werb 2002). Also, a limited number of studies showed that high levels of C-reactive protein (CRP) were associated with risk of colorectal cancer (Zhou et al. 2014) and higher prevalence of colorectal adenoma, a precancerous lesion of the

colorectal cancer (Godos et al. 2017).

Several studies reported that diet, age, body mass index (BMI), socioeconomic status, and physical activity were linked to inflammatory status (Chrysohoou et al. 2004; Barbaresko et al. 2013; Tabung et al. 2016; Shivappa, Steck, Hurley, Hussey, and Hebert 2014; Yudkin et al. 1999; Choi, Joseph, and Pilote 2013; Fedewa, Hathaway, and Ward-Ritacco 2017; Khera et al. 2005). Dietary factors in relation to inflammation have been identified in a number of studies exploring priori or posteriori dietary patterns (Chrysohoou et al. 2004; Barbaresko et al. 2013; Tabung et al. 2016; Shivappa, Steck, Hurley, Hussey, and Hebert 2014). Obesity was associated with elevated levels of CRP (Choi, Joseph, and Pilote 2013) and adipocytes synthesize and secrete IL-6 and CRP (Yudkin et al. 1999), whereas physical activity lowered levers of CRP (Fedewa, Hathaway, and Ward-Ritacco 2017). Also, CRP levels differed by age, race, and gender (Khera et al. 2005).

Two indices were developed to describe the overall effects of dietary factors on inflammation (Shivappa, Steck, Hurley, Hussey, and Hebert 2014; Tabung et al. 2016). These two indices were reported to be positively associated with colorectal cancer risk. A Dietary Inflammatory Index™ (DII®) has been recently developed based on the literature review of pro- or anti-inflammatory foods and nutrients (Shivappa, Steck, Hurley, Hussey, and Hebert 2014), and high scores of DII were positively associated with colorectal risk (Shivappa et al. 2017). Also, an empirically derived dietary pattern that reflected pro-inflammatory status was associated with colorectal cancer risk (Tabung et al. 2018).

In the current study, we developed models 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. Because CRP levels and factors associated with CRP levels may differ by sex, we developed the predicted hsCRP score in men and women separately or combined and compared the components and validities of indices. We further validated the predicted hsCRP score in an independent population, the colorectal adenoma study, and examined whether the predicted hsCRP score were associated with colorectal adenoma in Korean men and women.

II. Literature review

2.1 Statistics of colorectal cancer

Colorectal cancer was the third most frequently dignosed cancer with approximately 1.8 million reported cases in 2018 (Bray et al. 2018). The estimated age-standardized rates and mortality rates of colorectal cancer are, respectively, 19.7 per 100,000 cancer cases and 8.9 per mortality in 2018. The age-standardized rates of colorectal cancer in Korea were 44.5 per 100,000 cases, which was the second highest in the world after Hungary for both sexes (Bray et al. 2018). While the incidence and mortality rates of colorectal cancer in several Eastern European countries, Latin America, and Asia all have increased, those in highest human development index (HDI) countries such as Australia, Iceland, New Zealand and Japan have decreased due to improvements in cancer treatment and management (Arnold et al. 2017).

In Korea, the incidence of colorectal cancer increased from 1999 to 2010, then started to decrease slightly until 2015 (Jung et al. 2018). Also, age-standardized incidence rates for colorectal cancer was the second in men and the third in women and the fourth leading cause of cancer mortality in 2015 (Jung et al. 2018).

2.2 Dietary inflammatory index™ and empirical inflammatory dietary pattern

Dietary inflammatory index™ (DII®) and empirical dietary inflammatory pattern (EDIP) were developed to reflect the overall effects of dietary factors on inflammation (Shivappa, Steck, Hurley, Hussey, and Hebert 2014; Tabung et al. 2016). DII® is a literature-derived and population-based index, consisting of forty five foods and nutrients parameters. The inflammatory effect score of each parameter was calculated based on the results of previous studies which investigated the pro- or anti-inflammatory effects of each parameter in various study designs including cell culture, animals, and humans (Shivappa, Steck, Hurley, Hussey, and Hebert 2014). The DII® helped to predict hsCRP levels in the U.S. population-based observational study (Shivappa, Steck, Hurley, Hussey, Ma, et al. 2014).

EDIP is an empirically derived index that assesses the inflammatory potential of diets (Tabung et al. 2016). Reduced rank regression and stepwise linear regression were used to develop EDIP based on the inflammatory biomarkers, including Interleukin-6 (IL-6), CRP, and TNF-α receptor 2 (TNFαR2), and dietary data from the Nurses' Health Study (NHS). Validation study was performed by the two independent populations (Nurses' Health Study II (NHS-II) and the Health Professionals Follow-Up Study (HPFS)). In the validation study, all the relative concentrations of inflammatory biomarkers across quintiles of EDIP were statistically significant, indicating that EDIP assessed the inflammatory potential of the diet.

2.3 Inflammation and colorectal neoplasia

Chronic inflammation is thought to predispose individuals to cancer. Chronic inflammation may play an important role in colorectal neoplasia (Coussens and Werb 2002). For example, chronic inflammatory conditions, including Crohn's disease and chronic ulcerative colitis, risk factors for the development of colorectal carcinoma (Ullman and Itzkowitz 2011). Conversely, it was widely accepted that nonsteroidal anti-inflammatory drug use reduced the risk of colorectal cancer (González-Pérez, García Rodríguez, and López-Ridaura 2003). Colorectal adenomas were considered precursors to colorectal cancer through adenoma-carcinoma sequence (Fearon and Vogelstein 1990).

Sustained cell proliferation in inflammation and the constituents of microenvironment mediated by inflammatory cells promote development and progression of neoplasia (Terzic et al. 2010). Chronic inflammation due to the persistence of initiating factors or a failure in resolving inflammatory responses promotes tumor growth. Promoters induce cell proliferation, recruit inflammatory cells, and increase production of reactive oxygen species. Occurrence of oxidative DNA damage and reduction of DNA repair increase the potential of tumor initiation and growth (Coussens and Werb 2002).

Among the inflammatory cell components of tumors, tumor-associated macrophages (TAMs) are important for inflammatory infiltrates in neoplastic process. TAMs foster the spread of tumors by producing mediators that potentiate neoplastic progression including angiogenic and lymphanigogenic growth factors,

cytokines and proteases. And TAMs contribute to blunting the anti-tumor response by producing IL-10. Additionally, neutrophils, mast cells and activated T lymphocytes promote malignancies by releasing pro-angiogenic factors and chemokines (Coussens and Werb 2002).

Frequent infection may lead to chronic inflammation of the same area. Repeated tissue damage and the regeneration of tissue induce permanent genomic alterations, which is an expression of macrophage migration inhibitory factor (MIF). MIF suppresses transcriptional activity of p53 function. These chronic bypasses in managing functions of p53 might enhance proliferation and augments oncogenic alterations (Coussens and Werb 2002). Theses chronic inflammatory conditions, including inflammatory bowel disease, Crohn's disease, and chronic ulcerative colitis, are associated with colorectal carcinoma (Ullman and Itzkowitz 2011), suggesting a potential link between inflammation and colorectal cancer.

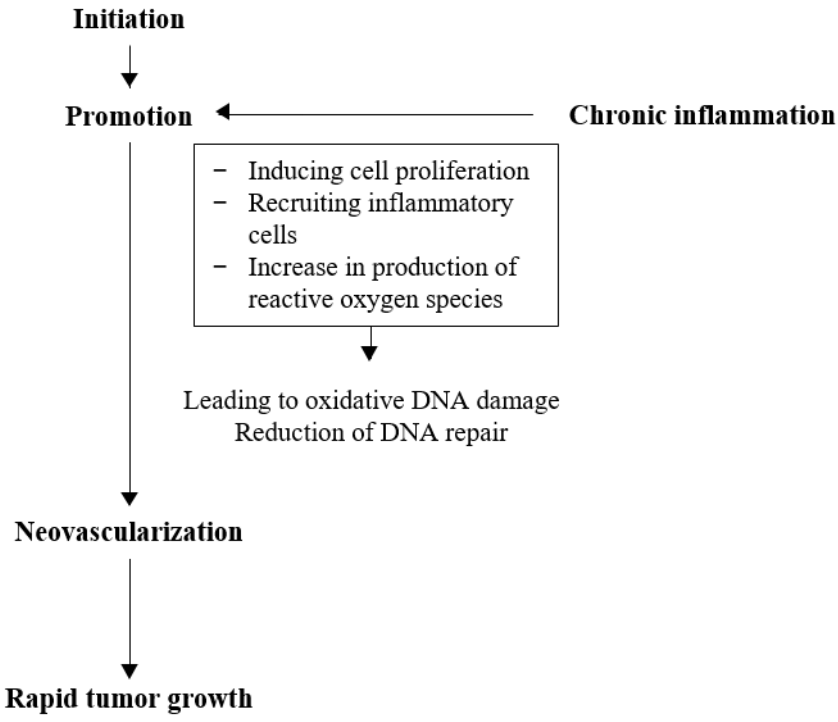

Figure 1. Pathways how chronic inflammation promotes tumor growth

2.4 The associations of CRP, DII, and EIDP with colorectal neoplasia

A meta-analysis of cross-sectional studies showed that high levels of CRP were associated with an increased risk of colorectal cancer (Zhou et al. 2014). The relative risk of 1-unit change in natural logarithm (ln) CRP was 1.12 (95% CI: 1.05, 1.21) based on cohort and nested-case control studies. The relative risks were found to be stronger in studies based on Asian population, which included studies performed on the Korean, Japanese, and Chinese populations, than in those based on Western population-based studies (Zhou et al. 2014).

A meta-analysis between CRP levels and colorectal adenoma reported that CRP levels were associated with increased risk or prevalence of colorectal adenoma, but were not statistically significant (OR: 1.23, 95% CI: 0.98, 1.54) (Godos et al. 2017). Elevated CRP levels were associated with increased prevalence of advanced adenoma. Also, the associations between CRP levels and non-advanced adenomas were inconsistent (OR: 1.06, 95% CI: 0.57, 1.98). It was reported that higher CRP levels were associated with increased prevalence of advanced colorectal adenomas in Japanese case-control study (Kigawa et al. 2017).

DII® was found to be positively associated with colorectal cancer in both case-control (OR: 1.73, 95% CI: 1.46, 2.05) and cohort (RR: 1.24, 95% CI: 1.15, 1.35) studies in a meta-analysis (Shivappa et al. 2017). Only one study, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, analyzed the associations between DII and colorectal adenoma (Haslam et al. 2017). In this cross-sectional

study, more inflammatory diets were associated with a higher prevalence of colorectal adenoma in men, not in women. Likewise, for EDIP, it was reported that higher EDIP scores, proinflammatory diets, were associated with increased risk of colorectal cancer in both men and women (Tabung et al. 2018).

III. Materials and methods

3.1 Schematic outline of the study

We developed models to predict hsCRP levels in the Health Examinee (HEXA) study and examined the association between the predicted hsCRP score and colorectal adenoma in the colorectal adenoma study. The schematic outline of the study is shown in Figure 2. The participants of HEXA study were randomly divided into two sets: 70% of the population was made a training set and 30% of the population was used as a testing set. The training set was used to develop the hsCRP score. The models were developed in men and women separately (men-specific and women-specific model) and combined (sex-combined model), as previous studies reported that levels of hsCRP and potential inflammatory determinants may differ by sex. The testing set was used to evaluate the validity of the predicted hsCRP score by comparing with the actual levels of hsCRP. Then, we examined the association between the predicted hsCRP score and colorectal adenoma in a separate population, the colorectal adenoma study.

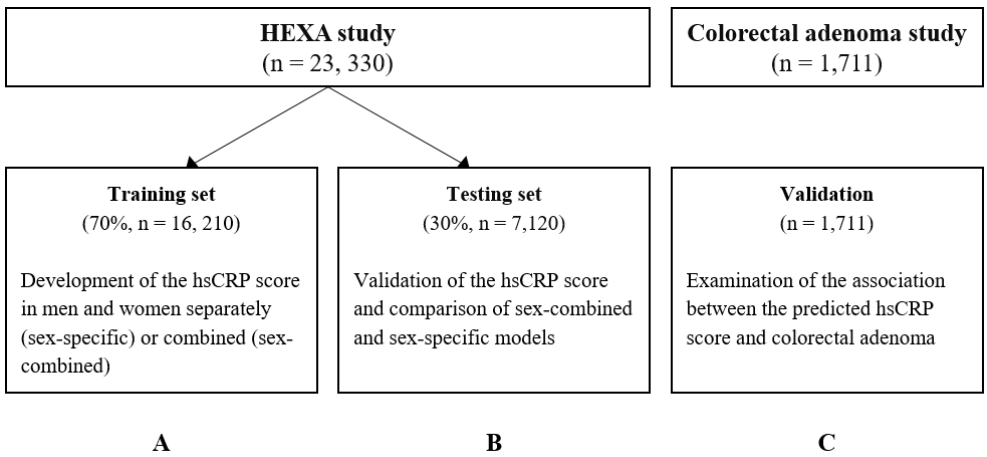

Figure 2. Schematic outline of the study.

A: training set of the HEXA study to develop the predicted hsCRP score, B: testing set to validate the predicted hsCRP score, C: Colorectal adenoma study, the separate population, to validate the predicted hsCRP score and examine the association with colorectal adenoma

3.2 Development of the predicted hsCRP score

3.2.1 Study Population

We developed the predicted hsCRP score for participants of the 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. Further information on its study design and protocol is available elsewhere (Kim, Han, and the Ko 2017). A total of 173,357 participants aged 40-79 years were enrolled in the HEXA Study from 2004 to 2013. In this study, we only included the 61,398 participants (41,743 men and 19,655 women) whose levels of hsCRP were measured with the same analyzer between January, 2004 and October, 2007. For the current study, 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) (Pearson Thomas et al. 2003). 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. Then we further excluded participants who had implausible energy intake (<800 or >4200 kcal per day for men, <500 or >3500 kcal per day for women, n = 1,257). The participants that remained (n = 39,470; 11,708 men and 27,762 women) were matched by exact age to adjust for the effects of age on hsCRP levels. As a result, a total of 23,330 participants (11,665 men and 11,665 women) from the HEXA Study were included. Figure 3 shows the flowchart for the inclusion of the participants. The study was reviewed and approved by the Institutional Review Board of Seoul National University (IRB No. E1811/001-009).

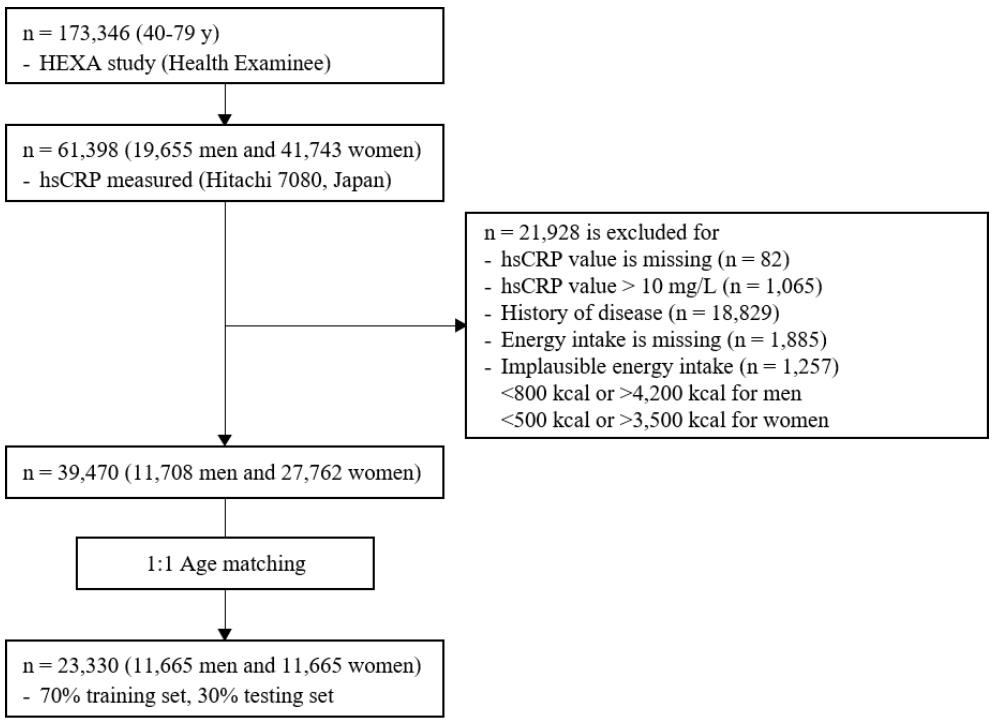

Figure 3. Study population from HEXA Study to develop the prediction model for hsCRP

3.2.2 Assessment of biomarker, anthropometric, sociodemographic and lifestyle factors in the HEXA study

Participants in the HEXA study were recruited at health examination centers and training hospitals in Korea. 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).

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, alcohol intake, smoking status, dietary habits, physical activities, and, for females, reproductive factors. Details of data collection are described elsewhere (Health Examinees Study 2015).

Body mass index (BMI) was calculated by dividing the participant's weight (kg) by the square of the height (m^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 workout types. For continuous variables, we assigned medians to missing values. For categorical variables, participants with missing values were assigned to reference groups. If a woman's menopausal status was not reported, we assumed that she was postmenopausal if she was 50 years or older.

3.2.3 Dietary assessment in the HEXA study

Participants completed 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 the FFQ validity was examined by comparing 3 dietary records every season, 12 dietary records in total (Ahn et al. 2007). 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. 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 or two 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 of the FFQ into 38 food groups based on similarity of nutritional characteristics or preparation method.

We calculated intakes of saturated fat, monounsaturated fatty acid, polyunsaturated fatty acid, flavan-3-ol, flavones, flavonols, anthocyanidins, and isoflavones by referring to the databases of the Rural Development Administration (RDA) (Rural Development Administration 2016), the Korea National Health and Nutrition Examination Survey (KNHANES) (Kweon et al. 2014) and the United States Department of Agriculture (USDA) (US Department of Agriculture, Agricultural Research Service, and Nutrient Data Laboratory 2015). Each nutrient was adjusted for energy intake using the residual method (Willett 2012).

3.2.4 Development of the predicted hsCRP score in the HEXA study

The 38 food groups, nutrients, alcohol intakes, BMI, smoking status, physical activities, educational levels and menopausal status of women were assessed at baseline to derive the prediction model of hsCRP because these factors were associated with inflammation (Chrysohoou et al. 2004; Barbaresko et al. 2013; Tabung et al. 2016; Shivappa, Steck, Hurley, Hussey, and Hebert 2014; Choi, Joseph, and Pilote 2013; Rom et al. 2013; Imhof et al. 2001; Garcia-Hermoso et al. 2016; Fedewa, Hathaway, and Ward-Ritacco 2017; Loucks et al. 2006; Sites et al. 2002). 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. We developed models in men and women separately (men-specific and women-specific model) and combined (sex-combined model) (Khera et al. 2005; Lee, Lee, et al. 2009). Four versions of the predicted hsCRP score were created: 1) foods only, 2) foods and nutrients, 3) foods and other lifestyles, and 4) foods, nutrients and other lifestyles.

For validation, the predicted hsCRP score were computed by multiplying the individual's response or estimated intake and the beta coefficient from the derived model in the testing set. Least-square mean (LS-mean) for quartiles of the predicted hsCRP score was calculated using the generalized linear model. Then relative concentrations and 95% confidence intervals (CIs) were calculated as ratios between

LS-mean levels of hsCRP among participants in each subsequent quartile of the predicted hsCRP score and the lowest quartile. The multivariate models were adjusted for age (continuous, years), alcohol intake (0, 0<-<15, 15-<30, ≥30 g/d for men, 0, 0<-<5, 5-<10, ≥10 g/d for women), smoking status (past, current, never for men, never and ever for women), regular physical exercise (none, 0<-< 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 or postmenopausal). The models were additionally adjusted for BMI (continuous, kg/m^2) in a sensitivity analysis.

3.3 Association between the predicted hsCRP score and colorectal adenoma

3.3.1 Study population

We examined the association between the predicted hsCRP score and colorectal adenoma in the colorectal adenoma study. Participants were 1,066 men and 661 women who underwent colonoscopies for regular health check-ups at Seoul National University Hospital Gangnam Center between May and December 2011. A detailed description of the study population is published elsewhere (Yang et al. 2016). We excluded patients who were diagnosed with colorectal cancer (n = 5); who had a medical history of colorectal cancer (n = 2); or whose energy intakes were not in a reasonable range (<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 subjects (1,056 men and 655 women) were included (Figure 4). Participants were defined 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. The sites of adenomas were categorized into proximal colon, distal colon or rectum. The proximal colon included the cecum, ascending colon, hepatic flexure and transverse colon, while the distal colon or rectum included the splenic flexure, descending colon, sigmoid colon and rectum. The study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1812-094-996).

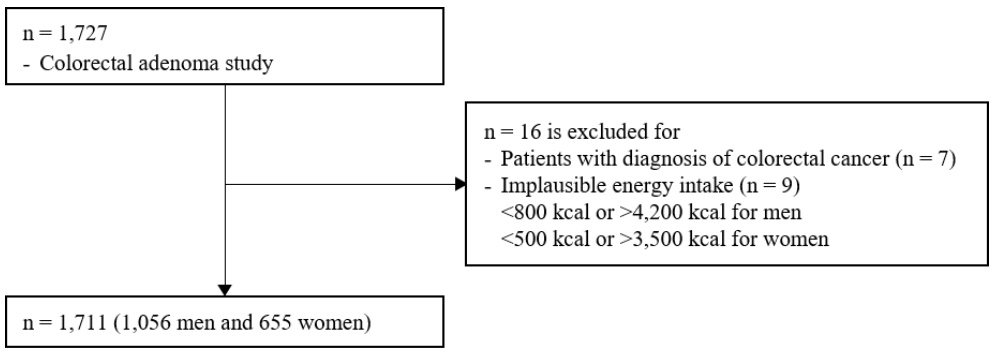

Figure 4. Study population from the colorectal adenoma study to examine the association between the predicted hsCRP score and colorectal adenoma

3.3.2 Assessment of biomarker, anthropometric, sociodemographic, lifestyle and dietary factors in the colorectal adenoma study

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. Body mass index (BMI) was calculated by dividing the participant's weight (kg) by the square of the height (m^2). Alcohol intake was estimated by summing up the ethanol weight after multiplying amounts and frequencies of specific types of liquors. To estimate dietary intakes, participants were asked about the amounts and frequencies of consumption of each food item by a dietitian using the same FFQs validated in KoGES (Ahn et al. 2007). We directly measured height, weight and waist circumference and calculated BMI. We measured serum hsCRP, and it was assessed using the ARCHITECT ci16200 (Abbott Laboratories, Abbott Park, IL, USA) automated immunoassay. The intra-assay coefficient of variation (CV) was less than 2%. Participants underwent colonoscopy on the same day when the questionnaire surveys, anthropometric measures and blood draw were conducted. According to the colonoscopy findings, participants diagnosed with colorectal adenoma were designated cases and those without any adenoma were designated non-cases.

3.3.3 Statistical analysis in the colorectal adenoma study

We computed the predicted hsCRP score by multiplying an individual's response or estimated intake and the beta coefficient derived from the HEXA study. We validated the prediction model among a subset of non-cases with hsCRP values (n=659) in the colorectal adenoma study by the relative concentrations of hsCRP levels according to the predicted hsCRP score. We calculated the LS-mean for quartiles of the predicted hsCRP score using the generalized linear model. Then, we calculated relative concentrations and 95% confidence intervals as ratios of LS-mean levels of hsCRP among participants in each subsequent quartile of the predicted hsCRP score to those among participants in the lowest quartile. To examine the associations of actual hsCRP levels and the predicted hsCRP score with colorectal adenoma, ORs and 95% CIs were calculated using logistic regression models. Study participants were categorized into quartiles according to the predicted hsCRP score and actual hsCRP levels, respectively. The characteristics of the colorectal adenoma study population were reported as the means with standard deviations for the continuous variables and as percentages for 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≥ g/day for women), smoking status (past, current, never for men and never and ever for women), physical activity (none, 0<-<14, ≥14 METs-hours/week), education levels (high school or less, university or above) and, in women only, menopausal status (premenopausal, postmenopausal). We further adjusted for BMI

(continuous, kg/m^2), 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. Potential effect modifiers were tested by including an interaction term of calculated score classified by median values of the predicted hsCRP score and age, BMI, waist circumference, smoking status, educational level, alcohol intake, physical activity and menopausal status in women. A likelihood ratio test was used to compare nested models that included cross-product terms with the original models that did not include terms. Polytomous logistic regression was used to conduct stratified analyses according to the progress and location of the colorectal adenoma, respectively, as we hypothesized that the magnitude of the associations may differ according to severity and anatomic sites. 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.

IV. Results

4.1 Development of the predicted hsCRP score

4.1.1 Components of the predicted hsCRP score

When we developed four versions of prediction model (Table 1-4). The components of the predicted hsCRP score based on foods are shown in Table 1. Fermented seafood and fruits were included in all three models; sex-combined, men-specific, and women-specific models. Ethanol, noodles/dumplings, other meats, and sweet potatoes were included in the sex-combined and men-specific, but not in the women-specific model. Beef, bread, pizza/hamburger, cake/snacks, chicken, and green tea were included in the sex-combined and women-specific, but not in the men-specific model.

In the sex-combined model, there were positive associations for intakes of ethanol, noodles/dumplings, fermented seafood, added sugar, other meats, beef, potatoes, and carbonated beverages and inverse associations for intakes of bread, pizza/hamburger, cake/snacks, sweet potatoes, chicken, green tea, and fruits. In the men-specific model, higher intakes of ethanol, noodles/dumplings, other meats, fermented seafood, and coffee and lower intakes of sweet potatoes and fruits were associated with increasing levels of hsCRP. Among women, higher intakes of mixed rice, beef, and fermented seafood and lower intakes of bread, pizza/hamburger, cake/snacks, chicken, green tea, and fruits were associated with higher levels of hsCRP.

When we developed predicted hsCRP model based on foods and nutrients, only fermented seafood was included in all three models (Table 2). In the sex-combined models, the higher intakes of omega 3, omega 6, ethanol, noodles/dumplings, sandwiches, potatoes, beef, other meats, fermented seafood, carbonated beverages, and coffee and lower intakes of flavanols, polyunsaturated fatty acid, pizza/hamburger, cake/snacks, sweet potatoes, chicken, and fruits were associated with increasing hsCRP levels. Among men, there were positive associations for ethanol, noodles/dumplings, other meats, fermented seafood, seaweeds, and coffee and inverse associations for flavanols, polyunsaturated fatty acid, and energy. Among women, there were positive associations for sandwiches, beef, and fermented seafood, and inverse associations for monounsaturated fatty acid, bread, pizza/hamburger, green tea, other beverages, and fruits.

When we developed the predicted hsCRP model based on foods and other lifestyle factors, age, BMI, and smoking status were selected in all three models (Table 3). Physical activity was included in the sex-combined and men-specific models. Education levels and menopausal status remained only in the women-specific model. Among dietary factors, higher intakes of ethanol, other grain, noodles/dumplings, potatoes, beef, and carbonated beverages and lower intakes of soup and stew with soybean paste/soybean paste, bread, and fruits were associated with higher levels of hsCRP in the sex-combined model. In the men-specific model, there were positive associations for ethanol, noodles/dumplings, potatoes, and coffee and inverse associations for soup and stew with soybean paste/soybean paste, sweet

potatoes, refined rice, and mixed rice. Among women, there were positive associations for intakes of beef and processed fish, and inverse associations for intakes of soup and stew with soybean paste/soybean paste, bread, and fish.

When we developed predicted hsCRP model based on foods, nutrients, and other lifestyle factors, the components and beta coefficients of the prediction model based on the foods, nutrients, and lifestyle related variables differed between the sex-combined model and sex-specific models (Table 4). Age, BMI, and smoking status were selected in all three models; sex-combined, men-specific, and women-specific models. Physical activity was included in the sex-combined and men-specific models, but not in the women-specific model. 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 ethanol, other grains (e.g., cereals), noodles/dumplings, potatoes, beef, and carbonated beverages and lower intakes of soup and stew with soybean paste/soybean paste, sweet potatoes, bread, and fruits in the sex-combined model. Dietary factors selected in the men-specific model were different from those in the women-specific model. Only soup and stew with soybean paste/soybean paste was inversely associated with hsCRP levels in both men and women. Among men only, there were positive associations for intakes of niacin and noodles/dumplings and inverse association for intake of sweet potatoes. In the women-specific model, in addition to intake of soup and stew with soybean paste/soybean paste, increasing intakes of beef and processed fish and decreasing intake of bread fish were associated with increasing levels of hsCRP.

Table 1. Components of the predicted hsCRP score based on foods in sex-combined and sex-specific model

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Positively associated								
Ethanol (g/day)	0.0019	<0.001	Ethanol (g/day)	0.0008	0.009	Mixed rice	0.0001	0.007
Noodles/dumplings	0.0004	<0.001	Noodles/dumplings	0.0003	0.004	Beef	0.0010	0.030
Fermented seafood	0.0087	<0.001	Other meats	0.0022	0.020	Fermented seafood	0.0085	0.007
Added sugar	0.0032	<0.001	Fermented seafood	0.0076	0.010			
Other meats	0.0019	0.008	Coffee	0.0111	< 0.001			
Beef	0.0012	<0.001						
Potatoes	0.0012	0.022						
Carbonated beverages	0.0003	0.032						
Negatively associated								
Bread	-0.0010	0.007	Sweet potatoes	-0.0016	0.030	Bread	-0.0014	0.003
Pizza/hamburger	-0.0029	<0.001	Fruits	-0.0001	0.015	Pizza/hamburger	-0.0038	0.001
Cake/snacks	-0.0011	0.033				Cake/snacks	-0.0018	0.014
Sweet potatoes	-0.0011	0.007				Chicken	-0.0041	0.015
Chicken	-0.0028	0.007				Green tea	-0.0003	0.001
Green tea	-0.0002	0.001				Fruits	-0.0001	<0.001
Fruits	-0.0002	<0.001						

Table 2. Components of the predicted hsCRP score based on foods and nutrients in sex-combined and sex-specific model

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Positively associated								
Omega 3	0.0381	0.049	Ethanol (g/day)	0.0008	0.009	Sandwiches	0.0028	0.024
Omega 6	0.1642	0.006	Noodles/dumplings	0.0005	<0.001	Beef	0.0016	0.001
Ethanol (g/day)	0.0018	<0.001	Other meats	0.0029	0.002	Fermented seafood	0.0077	0.014
Noodles/dumplings	0.0004	<0.001	Fermented seafood	0.0072	0.016			
Sandwiches	0.0027	0.006	Seaweeds	0.0124	0.009			
Potatoes	0.0011	0.036	Coffee	0.0124	<0.001			
Beef	0.0012	<0.001						
Other meats	0.0018	0.012						
Fermented seafood	0.0079	<0.001						
Carbonated beverages	0.0003	0.035						
Coffee	0.0078	<0.001						
Negatively associated								
Flavanols	-0.0117	<0.001	Flavanols	-0.0103	0.003	MUFA	-0.1112	<0.001
PUFA	-0.2369	<0.001	PUFA	-0.0339	0.015	Bread	-0.0013	0.011
Pizza/hamburger	-0.0025	0.001	Energy	-0.1749	<0.001	Pizza/hamburger	-0.0035	0.003
Cake/snacks	-0.0011	0.028				Green tea	-0.0002	0.007
Sweet potatoes	-0.0011	0.005				Other beverages	-0.0004	0.024
Chicken	-0.0029	0.006				Fruits	-0.0002	<0.001
Fruits	-0.0002	<0.001						

Table 3. Components of the predicted hsCRP score based on foods and lifestyle factors in sex-combined and sex-specific model

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Positively associated								
Ethanol (g/day)	0.0009	0.002	Ethanol (g/day)	0.0006	0.035	Beef	0.0009	0.040
Other grains	0.0015	0.035	Noodles/dumplings	0.0003	0.004	Processed fish	0.0028	0.013
Noodles/dumplings	0.0003	<0.001	Potatoes	0.0018	0.032	Age (years)	0.0140	<0.001
Potatoes	0.0012	0.016	Coffee	0.0055	0.042	BMI (1kg/m^2)	0.0782	<0.001
Beef	0.0011	<0.001	Age (years)	0.0113	<0.001	Smoking status		
Carbonated beverages	0.0003	0.018	BMI (1kg/m^2)	0.0714	<0.001	Never	Reference	
Age (years)	0.0158	<0.001	Smoking status			Past smoker	0.1514	0.056
BMI (1kg/m^2)	0.0773	<0.001	Never	Reference		Current smoker	0.1360	0.016
Smoking status			Past smoker	0.0334	0.117	Menopausal status		
Never	Reference		Current smoker	0.1894	<0.001	Premenopausal	Reference	
Past smoker	0.0787	<0.001				Perimenopausal	0.0587	0.043
Current smoker	0.2547	<0.001				Postmenopausal	0.1576	<0.001

Table 3. Components of the predicted hsCRP score based on foods and lifestyle factors in sex-combined and sex-specific model (continued)

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Negatively associated								
Soup and stew with soybean paste/ soybean paste	-0.0042	<0.001	Soup and stew with soybean paste /soybean paste	-0.0053	0.003	Soup and stew with soybean paste /soybean paste	-0.0033	0.031
Sweet potatoes	-0.0010	0.007	Sweet potatoes	-0.0017	0.017	Bread	-0.0010	0.020
Bread	-0.0007	0.035	Mixed rice	-0.0002	0.002	Fish	-0.0007	0.014
Fruits	-0.0001	0.020	Refined rice	-0.0001	0.024	Educational level		
Physical activities			Physical activities			Elementary school or below	Reference	
None	Reference		None	Reference		Middle school	-0.0659	0.010
0<-<3.5 times/d	-0.0586	<0.001	0<-<3.5 times/d	-0.1229	<0.001	High school	-0.0256	0.271
≥3.5 times/d	-0.0707	<0.001	≥3.5 times/d	-0.0933	<0.001	University or above	0.0247	0.395

Table 4. Components of the predicted hsCRP score based on foods, nutrients and lifestyle factors in sex-combined and sex-specific model

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Positively associated								
Ethanol (g/day)	0.0009	0.002	Niacin	0.1360	0.002	Beef	0.0009	0.040
Other grains	0.0015	0.035	Noodles/dumplings	0.0004	<0.001	Processed fish	0.0028	0.013
Noodles/dumplings	0.0003	<0.001	Age (years)	0.0113	<0.001	Age (years)	0.0140	<0.001
Potatoes	0.0012	0.016	BMI (1kg/m^2)	0.0707	<0.001	BMI (1kg/m^2)	0.0782	<0.001
Beef	0.0011	<0.001	Smoking status			Smoking status		
Carbonated beverages	0.0003	0.018	Never	Reference		Never	Reference	
Age (years)	0.0158	<0.001	Past smoker	0.0370	0.081	Past smoker	0.1514	0.056
BMI (1kg/m^2)	0.0773	<0.001	Current smoker	0.1990	<0.001	Current smoker	0.1360	0.016
Smoking status						Menopausal status		
Never	Reference					Premenopausal	Reference	
Past smoker	0.0787	<0.001				Perimenopausal	0.0587	0.043
Current smoker	0.2547	<0.001				Postmenopausal	0.1576	<0.001

Table 4. Components of the predicted hsCRP score based on foods, nutrients and lifestyle factors in sex-combined and sex-specific model (continued)

Sex-combined			Men-specific			Women-specific		
Variables	Beta	p value	Variables	Beta	p value	Variables	Beta	p value
Negatively associated								
Soup and stew with soybean paste/ soybean paste	-0.0042	<0.001	Soup and stew with soybean paste/ soybean paste	-0.0055	0.002	Soup and stew with soybean paste/ soybean paste	-0.0033	0.031
Sweet potatoes	-0.0010	0.007	Sweet potatoes	-0.0017	0.017	Bread	-0.0010	0.020
Bread	-0.0007	0.035	Exercise			Fish	-0.0007	0.014
Fruits	-0.0001	0.020	None	Reference		Educational level		
Physical activities			0<-<3.5 times/d	-0.1283	<0.001	Elementary school or below	Reference	
None	Reference		≥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
≥3.5 times/d	-0.0707	<0.001				University or above	0.0247	0.395

4.1.2 Relative concentrations of the actual levels of hsCRP according the quartiles of the predicted hsCRP score

Among models based on foods, the relative concentrations of the actual levels of hsCRP only increased according to increasing quartiles of the predicted hsCRP score among men (Table 5). Among men, the relative concentrations of the highest predicted hsCRP score compared to lowest were 1.12 (95% CI: 1.00, 1.26; p for trend = 0.006) in the sex-combined model and 1.22 (95% CI: 1.09, 1.36; p for trend <0.001) in the men-specific model. Among women, the actual hsCRP levels were likely to increase, but not statistically significant in sex-combined and there were not observed any trend in women-specific model.

Among models based on foods and nutrients, the relative concentrations of the actual levels of hsCRP only increased among men in sex-combined model (Table 6). Among men, the relative concentrations of the highest predicted hsCRP score compared to lowest were 1.16 (95% CI: 1.04, 1.30; p for trend <0.001) in the sex-combined model and 1.07 (95% CI: 0.96, 1.19; p for trend = 0.064) in the men-specific model (Table 6). Among women, the actual hsCRP levels were likely to increase, but not statistically significant in sex-combined and there were not observed any trend in women-specific model (Table 6).

Among models based on foods and lifestyle factors, the relative concentrations of the actual levels of hsCRP increased according to increasing quartiles of the predicted hsCRP score (Table 7). In the sex-combined model, the relative concentrations for the highest compared with the lowest predicted hsCRP score were

1.82 (95% CI: 1.66, 2.00; p for trend <0.001) for men and women combined, 1.64 (95% CI: 1.46, 1.83; p for trend <0.001) among men and 1.90 (95% CI: 1.65, 2.19; p for trend <0.001) among women. In 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 1.67 (95% CI: 1.50, 1.86; p for trend <0.001) among men and 2.02 (95% CI: 1.74, 2.34; p for trend <0.001) among women. When the models were further adjusted for BMI, the relative concentrations of the highest predicted hsCRP score were 1.24 (95% CI: 1.05, 1.48) among men and 1.14 (95% CI: 0.93, 1.41) among women in sex-specific models.

The relative concentrations of the actual levels of hsCRP increased according to increasing quartiles of the predicted hsCRP score using foods, nutrients and lifestyle factors (Table 8). Comparing the models using foods, nutrients and lifestyle factors with the models using foods and lifestyle factors, only the components of the men-specific models were changed. The relative concentrations comparing between the highest predicted hsCRP score and the lowest predicted hsCRP score were 1.65 (95% CI: 1.49, 1.84; p for trend <0.001) among men. When BMI was further adjusted for, the relative concentrations of the highest predicted hsCRP score compared to the lowest were 1.17 (95% CI: 0.98, 1.40) in men-specific models.

Table 5. Relative concentrations and 95% confidence intervals between the predicted hsCRP score using foods and actual hsCRP levels in the testing set of the HEXA

	Quartiles of the the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Sex-combined model (n = 7,108)					
Age, sex adjusted model	Reference	1.03 (0.96, 1.11)	1.08 (1.01, 1.17)	1.16 (1.08, 1.25)	<0.001
Multivariate adjusted model[a]	Reference	1.02 (0.92, 1.12)	1.06 (0.96, 1.16)	1.10 (1.01, 1.21)	0.001
Men in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.05 (0.94, 1.16)	1.11 (1.00, 1.24)	1.19 (1.07, 1.32)	<0.001
Multivariate adjusted model[b]	Reference	1.02 (0.91, 1.14)	1.07 (0.96, 1.20)	1.12 (1.00, 1.26)	0.006
Women in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.02 (0.92, 1.13)	1.03 (0.92, 1.14)	1.04 (0.94, 1.16)	0.249
Multivariate adjusted model[c]	Reference	1.02 (0.89, 1.17)	1.02 (0.89, 1.17)	1.05 (0.92, 1.20)	0.230
Men-specific model (n = 3,560)					
Age-adjusted model	Reference	1.07 (0.97, 1.19)	1.18 (1.06, 1.30)	1.29 (1.17, 1.43)	<0.001
Multivariate adjusted model[b]	Reference	1.06 (0.95, 1.18)	1.13 (1.02, 1.26)	1.22 (1.09, 1.36)	<0.001
Women-specific model (n = 3,560)					
Age-adjusted model	Reference	0.98 (0.88, 1.08)	0.97 (0.87, 1.08)	1.00 (0.90, 1.11)	0.846
Multivariate adjusted model[c]	Reference	0.97 (0.85, 1.11)	0.96 (0.84, 1.10)	0.99 (0.86, 1.13)	0.601

[a] 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above)

[c] Adjusted for age (continuous, years), alcohol (0, 0<-<5, 5-<10, 10≥ g/d), smoking status (ever, never), regular physical exercise (none, 0<-<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 (premenopausal, perimenopausal, postmenopausal)

Table 6. Relative concentrations and 95% confidence intervals between the predicted hsCRP score using foods and nutrients and actual hsCRP levels in the testing set of the HEXA

	Quartiles of the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Sex-combined model (n = 7,108)					
Age, sex adjusted model	Reference	1.04 (0.96, 1.12)	1.11 (1.03, 1.20)	1.15 (1.07, 1.25)	<0.001
Multivariate adjusted model[a]	Reference	1.03 (0.94, 1.13)	1.09 (0.99, 1.19)	1.09 (1.00, 1.19)	0.001
Men in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.07 (0.97, 1.19)	1.13 (1.02, 1.25)	1.23 (1.11, 1.37)	<0.001
Multivariate adjusted model[b]	Reference	1.05 (0.94, 1.18)	1.09 (0.97, 1.21)	1.16 (1.04, 1.30)	<0.001
Women in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.00 (0.90, 1.11)	1.05 (0.95, 1.17)	1.04 (0.93, 1.15)	0.219
Multivariate adjusted model[c]	Reference	1.00 (0.87, 1.14)	1.05 (0.91, 1.20)	1.04 (0.91, 1.18)	0.232
Men-specific model (n = 3,560)					
Age-adjusted model	Reference	1.02 (0.92, 1.14)	1.08 (0.98, 1.20)	1.16 (1.05, 1.29)	<0.001
Multivariate adjusted model[b]	Reference	1.00 (0.90, 1.12)	1.03 (0.93, 1.15)	1.07 (0.96, 1.19)	0.064
Women-specific model (n = 3,560)					
Age-adjusted model	Reference	0.94 (0.85, 1.04)	1.01 (0.91, 1.12)	0.96 (0.86, 1.07)	0.589
Multivariate adjusted model[c]	Reference	0.94 (0.82, 1.07)	1.00 (0.88, 1.15)	0.95 (0.82, 1.09)	0.374

[a] 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above)

[c] Adjusted for age (continuous, years), alcohol (0, 0<-<5, 5-<10, 10≥ g/d), smoking status (ever, never), regular physical exercise (none, 0<-<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 (premenopausal, perimenopausal, postmenopausal)

Table 7. Relative concentrations and 95% confidence intervals between the predicted hsCRP score using foods and lifestyle factors and actual hsCRP levels in the testing set of the HEXA

	Quartiles of the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Sex-combined model (n = 7,108)					
Age, sex adjusted model	Reference	1.30 (1.21, 1.41)	1.55 (1.44, 1.67)	1.84 (1.70, 1.99)	<0.001
Multivariate adjusted model[a]	Reference	1.30 (1.18, 1.43)	1.54 (1.41, 1.69)	1.82 (1.66, 2.00)	<0.001
Men in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.27 (1.15, 1.41)	1.35 (1.21, 1.49)	1.68 (1.51, 1.86)	<0.001
Multivariate adjusted model[b]	Reference	1.26 (1.13, 1.41)	1.32 (1.19, 1.48)	1.64 (1.46, 1.83)	<0.001
Women in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.27 (1.14, 1.42)	1.44 (1.30, 1.60)	1.85 (1.65, 2.07)	<0.001
Multivariate adjusted model[c]	Reference	1.28 (1.12, 1.47)	1.46 (1.27, 1.67)	1.90 (1.65, 2.19)	<0.001
Men-specific model (n = 3,560)					
Age-adjusted model	Reference	1.25 (1.13, 1.38)	1.33 (1.20, 1.47)	1.70 (1.54, 1.88)	<0.001
Multivariate adjusted model[b]	Reference	1.24 (1.11, 1.38)	1.31 (1.18, 1.45)	1.67 (1.50, 1.86)	<0.001
Women-specific model (n = 3,560)					
Age-adjusted model	Reference	1.25 (1.12, 1.39)	1.51 (1.35, 1.69)	1.97 (1.75, 2.21)	<0.001
Multivariate adjusted model[c]	Reference	1.27 (1.11, 1.47)	1.55 (1.35, 1.79)	2.02 (1.74, 2.34)	<0.001

[a] 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above)

[c] Adjusted for age (continuous, years), alcohol (0, 0<-<5, 5-<10, 10≥ g/d), smoking status (ever, never), regular physical exercise (none, 0<-<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 (premenopausal, perimenopausal, postmenopausal)

Table 8. Relative concentrations and 95% confidence intervals between the predicted hsCRP score using foods, nutrients and lifestyle factors and actual hsCRP levels in the testing set of the HEXA

	Quartiles of the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Sex-combined model (n = 7,108)					
Age, sex adjusted model	Reference	1.30 (1.21, 1.41)	1.55 (1.44, 1.67)	1.84 (1.70, 1.99)	<0.001
Multivariate adjusted model[a]	Reference	1.30 (1.18, 1.43)	1.54 (1.41, 1.69)	1.82 (1.66, 2.00)	<0.001
Men in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.27 (1.15, 1.41)	1.35 (1.21, 1.49)	1.68 (1.51, 1.86)	<0.001
Multivariate adjusted model[b]	Reference	1.26 (1.13, 1.41)	1.32 (1.19, 1.48)	1.64 (1.46, 1.83)	<0.001
Women in sex-combined model (n = 3,554)					
Age-adjusted model	Reference	1.27 (1.14, 1.42)	1.44 (1.30, 1.60)	1.85 (1.65, 2.07)	<0.001
Multivariate adjusted model[c]	Reference	1.28 (1.12, 1.47)	1.46 (1.27, 1.67)	1.90 (1.65, 2.19)	<0.001
Men-specific model (n = 3,560)					
Age-adjusted model	Reference	1.21 (1.10, 1.34)	1.28 (1.16, 1.42)	1.69 (1.52, 1.86)	<0.001
Multivariate adjusted model[b]	Reference	1.20 (1.08, 1.34)	1.26 (1.14, 1.41)	1.65 (1.49, 1.84)	<0.001
Women-specific model (n = 3,560)					
Age-adjusted model	Reference	1.25 (1.12, 1.39)	1.51 (1.35, 1.69)	1.97 (1.75, 2.21)	<0.001
Multivariate adjusted model[c]	Reference	1.27 (1.11, 1.47)	1.55 (1.35, 1.79)	2.02 (1.74, 2.34)	<0.001

[a] 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, 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, 0<-<3.5 times per week, ≥3.5 times per week), educational level (elementary school or below, middle school, high school, university or above)

[c] Adjusted for age (continuous, years), alcohol (0, 0<-<5, 5-<10, 10≥ g/d), smoking status (ever, never), regular physical exercise (none, 0<-<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 (premenopausal, perimenopausal, postmenopausal)

4.2 Association between the predicted hsCRP score and colorectal adenoma

4.2.1 General characteristics of participants

The general characteristics of men and women by quartiles of the predicted hsCRP score are presented in Table 9 and 10. 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 (Table 9). Women who had the higher predicted hsCRP score tended to be older, postmenopausal and to have higher BMI and less percent of university or above education compared to those with lower scores (Table 10).

Table 9. Characteristics by quartiles of the predicted hsCRP score of men-specific models using foods, nutrients and lifestyle factors among men in the colorectal adenoma study

	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, mean ± SD	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 stats, n (%)				
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/m^2, mean ± SD	21.9 ± 1.8	23.8 ± 1.4	25.1 ± 1.6	27.2 ± 2.0
Educational level, n (%)				
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, n (%)				
0g	22 (8.5)	25 (9.7)	32 (12.7)	30 (11.8)
0g< - <15g	109 (42.1)	87 (33.7)	66 (26.1)	74 (29.0)
15g≤ - <30g	55 (21.2)	59 (22.9)	64 (25.3)	50 (19.6)
30g≤	73 (28.2)	87 (33.7)	91 (36.0)	101 (39.6)
Exercise, n (%)				
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)

Table 10. Characteristics by quartiles of the predicted hsCRP score of women-specific models using foods, nutrients and lifestyle factors among women in the colorectal adenoma study

	Quartiles of the predicted hsCRP score			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
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, mean ± SD	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, n (%)				
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)	5 (3.1)	3 (1.9)	9 (5.6)
Post-menopausal status, n (%)	8 (5.1)	51 (31.9)	108 (67.5)	136 (84.0)
BMI, kg/m^2, mean ± SD	19.4 ± 1.3	21.2 ± 1.6	22.3 ± 1.8	25.3 ± 3.1
Educational level, n (%)				
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, n (%)				
0g	66 (42.3)	67 (42.4)	73 (46.5)	93 (60.0)
0g< - <15g	77 (49.4)	70 (44.3)	71 (45.2)	47 (30.3)
15g≤ - <30g	7 (4.5)	9 (5.7)	8 (5.1)	10 (6.5)
30g≤	6 (3.9)	12 (7.6)	5 (3.2)	5 (3.2)
Exercise, n (%)				
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)

4.2.2 Relative concentrations of the actual hsCRP levels according to the quartiles of the predicted hsCRP score

When the relative concentrations of actual hsCRP levels were estimated in the colorectal adenoma study, the relative concentrations comparing participants with the highest predicted hsCRP score and the lowest predicted hsCRP score were 1.92 (95% CI: 1.20, 3.07; p for trend <0.001) among men and 3.64 (95% CI: 1.95, 6.79; p for trend <0.001) among women (Table 11).

Table 11. Relative concentrations and 95% confidence intervals between the predicted hsCRP score of men-specific and women-specific models using foods, nutrients and lifestyle factors and actual hsCRP levels among non-case participants in the colorectal adenoma study

	Quartiles of the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Men (n=361)					
Age-adjusted model	Reference	1.43 (0.96, 2.13)	1.66 (1.09, 2.52)	1.79 (1.15, 2.77)	<0.001
Multivariate adjusted model[a]	Reference	1.46 (0.95, 2.23)	1.81 (1.15, 2.83)	1.92 (1.20, 3.07)	<0.001
Women (n=298)					
Age-adjusted model	Reference	1.53 (0.92, 2.57)	1.84 (1.11, 3.07)	3.18 (1.81, 5.61)	<0.001
Multivariate adjusted model[b]	Reference	1.61 (0.91, 2.86)	1.99 (1.13, 3.49)	3.64 (1.95, 6.79)	<0.001

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<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≥ g/d), smoking status (past/current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

4.2.3 Associations between the actual hsCRP levels and colorectal adenoma

We found that increasing levels of actual hsCRP were associated with increasing prevalence of colorectal adenoma in men and women (Table 12). The ORs of the highest quartiles of the predicted hsCRP score compared with the lowest were 1.66 (95% CI: 1.02, 2.70; p for trend = 0.043) among men and 2.81 (95% CI: 1.29, 6.13; p for trend = 0.005) among women.

Table 12. Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal adenoma according to quartiles of actual hsCRP levels

	Quartiles of the actual hsCRP levels				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Men (n=602)					
Number of case/non-case	46/101	60/90	66/82	69/88	
Age-adjusted model	Reference	1.40 (0.86, 2.28)	1.70 (1.05, 2.76)	1.63 (1.01, 2.63)	0.049
Multivariate adjusted model[a]	Reference	1.39 (0.85, 2.27)	1.73 (1.06, 2.82)	1.66 (1.02, 2.70)	0.043
Women (n=391)					
Number of case/non-case	12/76	24/93	23/70	34/59	
Age-adjusted model	Reference	1.36 (0.63, 2.95)	1.58 (0.72, 3.50)	2.74 (1.27, 5.88)	0.004
Multivariate adjusted model[b]	Reference	1.43 (0.65, 3.15)	1.58 (0.70, 3.55)	2.81 (1.29, 6.13)	0.005

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<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≥ g/d), smoking status (past/current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

4.2.4 Associations between the predicted hsCRP scores and colorectal adenoma

We found that the increasing predicted hsCRP score were associated with increasing prevalence of colorectal adenoma (Table 13). Compared with participants in the lowest quartile, the ORs of colorectal adenoma among those at 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 models were further adjusted for BMI, ORs which compared the highest quartiles with the lowest quartiles of the predicted hsCRP score were attenuated to 0.98 (95% CI: 0.42, 2.31; p for trend = 0.974) in men and 1.61 (95% CI: 0.46, 5.64; p for trend = 0.512) in women.

Table 13. 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 using foods, nutrients and lifestyle factors

	Quartiles of the predicted hsCRP score				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend
Men (n=1,056)					
Number of case/non-case	75/189	98/166	110/154	123/141	
Age-adjusted model	Reference	1.27 (0.87, 1.85)	1.46 (1.00, 2.12)	1.63 (1.12, 2.38)	0.009
Multivariate adjusted model[a]	Reference	1.30 (0.89, 1.91)	1.52 (1.02, 2.27)	1.71 (1.12, 2.62)	0.011
Women (n=655)					
Number of case/non-case	24/139	30/134	37/127	58/106	
Age-adjusted model	Reference	2.03 (1.01, 4.06)	2.97 (1.44, 6.10)	3.15 (1.44, 6.91)	0.007
Multivariate adjusted model[b]	Reference	1.88 (0.93, 3.81)	2.87 (1.36, 6.03)	2.86 (1.26, 6.49)	0.019

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<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≥ g/d), smoking status (past/current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

4.2.5 Associations between the actual hsCRP levels and colorectal adenoma, stratified by risk factors

We examined whether the associations between the predicted hsCRP score of men-specific and women-specific models using foods, nutrients and lifestyle factors and colorectal adenoma were modified by risk factors (Table 14 and 15). Significant differences were not shown when we stratified participants by age, BMI, waist circumference, smoking status, educational level, alcohol intake and physical activity in men (Table 14).

The interactions of age, educational level and menopausal status were significant among women (Table 15). When women were stratified by age (<50 or ≥50 years), the ORs were 3.74 (95% CI: 1.77, 7.90) for women who were under fifty years and 1.09 (95% CI: 0.57, 2.07) for women who were fifty years or older (p for interaction = 0.014). The ORs of groups equal to and more than median values of the predicted hsCRP score, compared to under the median values, were 0.66 (95% CI: 0.26, 1.67) for women whose educational levels were high school diploma or below and 2.81 (95% CI: 1.49, 5.31) for women whose educational levels were university or above (p for interaction = 0.028). The ORs of those groups equal to and more than median values compared to 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).

Table 14. Odds ratios (ORs) and 95% confidence intervals (CIs) according to the dichotomous category of the predicted hsCRP score of men-specific models using foods, nutrients and lifestyle factors, stratified by risk factors among men

	Dichotomous category of the predicted hsCRP score				
	< median		≥ median		
	No. cases/ non-cases	OR (95% CI)	No. cases/ non-cases	OR (95% CI)	*p* for interaction
Men[a]	173/355		233/295		
Age					
< 52 years, median	79/221	Reference	72/137	1.41 (0.91, 2.20)	0.801
≥ 52 years	94/134	Reference	161/158	1.42 (0.97, 2.10)	
BMI					
< 23 kg/m^2	82/173	Reference	10/12	1.35 (0.45, 4.03)	0.825
≥ 23 kg/m^2	90/177	Reference	211/281	1.14 (0.79, 1.65)	
Waist circumference					
< 90 cm	151/309	Reference	77/110	1.10 (0.72, 1.70)	0.208
≥ 90 cm	21/41	Reference	143/183	1.19 (0.63, 2.26)	
Smoking status					
non-smoker	56/114	Reference	42/50	1.30 (0.71, 2.37)	0.716
current/past smoker	115/236	Reference	188/239	1.41 (1.01, 1.97)	
Education level					
high school or below	18/41	Reference	43/43	2.23 (0.96, 5.21)	0.219
university or above	150/302	Reference	180/236	1.34 (0.98, 1.84)	

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), and educational level (high school or below, university or above)

Table 14. Odds ratios (ORs) and 95% confidence intervals (CIs) according to the dichotomous category of the predicted hsCRP score of men-specific models using foods, nutrients and lifestyle factors, stratified by risk factors among men (continued)

	Dichotomous category of the predicted hsCRP score				
	< median		≥ median		
	No. cases/ non-cases	OR (95% CI)	No. cases/ non-cases	OR (95% CI)	*p* for interaction
Men[a]	173/355		233/295		
Alcohol intake					
0g/d	14/33	Reference	31/33	1.95 (0.72, 5.28)	0.284
0<-<15 g/d	59/137	Reference	63/77	1.94 (1.12, 3.34)	
≥ 15g/d	97/177	Reference	133/173	1.22 (0.83, 1.78)	
Physical activities					
none	37/112	Reference	103/138	1.70 (1.02, 2.84)	0.977
0<-< 14 METs-hours/week	57/82	Reference	26/47	0.69 (0.35, 1.35)	
≥ 14 METs-hours/week	77/155	Reference	98/102	1.72 (1.11, 2.65)	

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), and educational level (high school or below, university or above)

Table 15. Odds ratios (ORs) and 95% confidence interval (CIs) according to the dichotomous category of the predicted hsCRP score of women-specific models using foods, nutrients and lifestyle factors, stratified by risk factors among women

	Dichotomous category of the predicted hsCRP score				
	< median		≥ median		
	No. cases/ non-cases	OR (95% CI)	No. cases/ non-cases	OR (95% CI)	*p* for interaction
Women[a]	45/282		104/224		
Age					
< 50 years, median	26/220	Reference	19/40	3.74 (1.77, 7.90)	0.014
≥ 50 years	19/62	Reference	85/184	1.09 (0.57, 2.07)	
BMI					
< 23 kg/m^2	42/260	Reference	41/97	0.88 (0.43, 1.80)	0.194
≥ 23 kg/m^2	2/19	Reference	61/118	4.15 (0.85, 20.31)	
Waist circumference					
< 80 cm	34/212	Reference	25/57	0.89 (0.39, 2.02)	0.651
≥ 80 cm	10/67	Reference	77/158	3.17 (1.40, 7.18)	
Smoking status					
Non-smoker	40/254	Reference	92/204	1.79 (1.05, 3.06)	0.519
Current/past smoker	4/24	Reference	9/18	1.69 (0.28, 10.13)	
Education level					
High school or below	16/47	Reference	37/72	0.66 (0.26, 1.67)	0.028
University or above	26/220	Reference	59/137	2.81 (1.49, 5.31)	

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15≥ g/d), regular physical exercise (none, 0<-< 14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

Table 15. Odds ratios (ORs) and 95% confidence interval (CIs) according to the dichotomous category of the predicted hsCRP score of women-specific models using foods, nutrients and lifestyle factors, stratified by risk factors among women (continued)

	Dichotomous category of the predicted hsCRP score				
	< median		≥ median		
	No. cases/ non-cases	OR (95% CI)	No. cases/ non-cases	OR (95% CI)	*p* for interaction
Women[a]	45/282		104/224		
Alcohol intake					
0g/d	23/110	Reference	51/115	0.84 (0.40, 1.76)	0.407
0<-<15 g/d	13/134	Reference	36/82	3.88 (1.63, 9.22)	
≥ 15g/d	7/27	Reference	10/18	1.25 (0.24, 6.48)	
Physical activities					
None	19/128	Reference	53/106	2.52 (1.19, 5.35)	0.463
0<-< 14 METs-hours/week	4/58	Reference	15/45	3.57 (0.76, 16.78)	
≥ 14 METs-hours/week	19/90	Reference	30/69	1.18 (0.50, 2.79)	
Menopausal status					
Premenopausal	26/232	Reference	26/52	4.21 (2.12, 8.36)	<0.001
Postmenopausal	18/41	Reference	74/170	0.71 (0.36, 1.41)	

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15≥ g/d), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

4.2.6 Associations between the actual hsCRP levels and colorectal adenoma, stratified by progress and location

We further examined the association between the predicted hsCRP score and colorectal adenoma according to progressive stage and location (Table 16). The predicted hsCRP scores appeared to be positively associated with the prevalence of colorectal adenoma in those with advanced adenoma in both men (OR: 1.62, 95% CI: 1.00, 2.63) and women (OR: 6.55, 95% CI: 1.62, 26.37), but not in those with non-advanced adenoma. When analyses were stratified by location, the predicted hsCRP scores were positively associated with the prevalence of distal colon and rectal adenoma in men and proximal colon in women. Men with median or higher levels of the predicted hsCRP score had a 1.83 times higher prevalence of distal colon and rectal adenoma compared to those with lower than median. Women at median or above median values of the predicted hsCRP score had a 1.95 times higher prevalence of proximal colon adenoma compared to those with under median.

Table 16. Odds ratios (OR) and 95% confidence interval (CI) according to the predicted hsCRP score of men-specific and women-specific models using foods, nutrients and lifestyle factors, stratified by progression and anatomical site

	Dichotomous category of the predicted hsCRP score			
	< median		≥ median	
	No. cases/non-cases	OR (95% CI)	No. cases/non-cases	OR (95% CI)
Men[a]	173/355		233/295	
Non-advanced	137/355	Reference	155/295	1.30 (0.95, 1.79)
Advanced	36/355	Reference	78/295	1.62 (1.00, 2.63)
Proximal colon	121/355	Reference	131/295	1.16 (0.83, 1.62)
Distal colon and rectum	52/355	Reference	102/295	1.83 (1.21, 2.77)
Women[b]	45/282		104/224	
Non-advanced	42/282	Reference	80/224	1.49 (0.87, 2.55)
Advanced	3/282	Reference	24/224	6.55 (1.62, 26.37)
Proximal colon	23/282	Reference	62/224	1.95 (1.02, 3.75)
Distal colon and rectum	22/282	Reference	42/224	1.65 (0.82, 3.33)

[a] Adjusted for age (continuous, years), alcohol (0, 0<-<15, 15-<30, 30≥ g/d), smoking status (past, current, never), regular physical exercise (none, 0<-<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 ≥ g/d), smoking status (past/current, never), regular physical exercise (none, 0<-<14 METs-hours/week, ≥14 METs-hours/week), educational level (high school or below, university or above), and menopausal status (premenopausal, postmenopausal)

V. Discussion

In the present study, we derived a prediction model for chronic inflammatory status. The predicted hsCRP score were correlated with actual hsCRP levels in the colorectal adenoma study participants, suggesting the predicted hsCRP score may be suited to reflect inflammatory status in Korean adult populations. Men and women with the increasing predicted hsCRP score had higher prevalence of colorectal adenoma compared to those with low scores. The associations were more pronounced among women who aged less than 50 years, whose educational levels were university or above or who were premenopausal. Men and women with the higher predicted hsCRP score 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 observed that the higher values of actual hsCRP and predicted hsCRP score were associated with colorectal adenoma in both men and women. Chronic inflammation make contributions to development and progression of cancer (Mantovani et al. 2008). Chronic inflammation activates the transcription factors such as NF-κB and signal transducer and activator of transcription 3 (STATA3) of tumor cells. These activated transcription factors stimulate to produce cytokines and chemokines. These cytokines and chemokines recruit various leukocytes, resulting in cell proliferation, promoting angiogenesis and lymphangiogenesis and invasion of tumor cells. A recent meta-analysis has revealed that elevated CRP levels were

associated with colorectal cancer (Zhou et al. 2014) and colorectal advanced adenoma (Godos et al. 2017). The DII™ was developed based on the literature review (Shivappa, Steck, Hurley, Hussey, and Hebert 2014) and was found to be associated with colorectal adenoma (Haslam et al. 2017) and colorectal cancer (Shivappa et al. 2017). Tabung developed and validated an empirical dietary inflammatory pattern (EDIP) (Tabung et al. 2016; Tabung et al. 2017) and reported that higher EDIP scores were associated with risk of colorectal cancer (the hazard ratios (HRs) of quintile 5 compared to quintile 1 were 1.62 (95% CI: 1.05, 2.49, p for trend 0.002) among men and 1.33 (95% CI: 0.97, 1.81, p for trend 0.030) among women) (Tabung et al. 2018). Also, Korean studies derived dietary patterns using reduced rank regression and examined association with between dietary pattern scores based on CRP levels and colorectal adenoma in case-control study (Cho et al. 2016). The Korean case-control study reported that higher dietary pattern scores, which was associated with high levels of CRP, were positively associated with prevalence of colorectal cancer.

In our predicted hsCRP models, BMI, age, and smoking status were selected as a determinants for hsCRP levels in both men and women. The condition of obesity is associated with chronic inflammation (Choi, Joseph, and Pilote 2013). Adipose tissues produce inflammation-related factors such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and adiponectin (Karastergiou and Mohamed-Ali 2010). The overexpression of pro-inflammatory cytokines and IL-6 stimulates hepatocytes to produce CRP, driving the systemic inflammation in the

body (Ellulu et al. 2017). Smoking has a pro-inflammatory effect by activating the NF-κB pathway and has been reported to be a risk factor for various chronic diseases (Lee, Taneja, and Vassallo 2012). In our study, having higher BMI and being current smoker were associated with elevated hsCRP levels.

Also, 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 men (Wannamethee et al. 2002). Regular exercise was reported to reduce toll-like receptor 4 (TLR4) expression and lower lipopolysaccharide-stimulated IL-6 production (Stewart et al. 2005). Additionally, participants whose educational levels were college or above, compared to those whose educational levels were high school graduates, were associated with lower CRP levels (Loucks et al. 2006). We found that being postmenopausal was positively associated with hsCRP levels. The Women's Health Study has reported on physiologic changes through the menopause transition and found inflammatory markers increased from being premenopausal to postmenopausal (Lee, Carr, et al. 2009).

Among dietary factors, higher intakes of noodles/dumplings in sex-combined and men-specific models and beef in sex-combined and women-specific models and lower intakes of soybean paste/soup and stew with soybean paste in all three models, sweet potatoes in sex-combined and men-specific and breads with red bean or cream filling in sex-combined and women-specific models were associated with elevated levels of hsCRP. EDIP reported that higher intakes of red meat and lower intakes of

dark yellow vegetables including sweet potatoes were associated with increasing levels of CRP, IL-6, and TNF-α (Tabung et al. 2016). In German and U.S. studies, soy foods and legumes were inversely associated with inflammatory biomarkers (Nettleton et al. 2007; Heidemann et al. 2005). Inconsistent relationships between glycemic load and inflammatory markers were reported in randomized controlled trials (Milajerdi et al. 2018). Likewise, in our study, the relationships between high levels of hsCRP levels and the components of foods related high glycemic load were inconsistent. Among high glycemic foods, the intakes of noodles were positively associated with hsCRP levels in sex-combined and men-specific models, whereas the intakes of bread with red bean or cream filling were inversely associated with hsCRP levels in sex-combined and women-specific models.

When we compared the sex-combined and sex-specific models, the components of the prediction models and the magnitude of the relative concentrations differed by sex. Although differences of CRP by sex are controversial, it was reported that levels of hsCRP in women were higher than men in the U.S. population (Lakoski et al. 2006; Khera et al. 2005). In contrast, men had higher CRP levels than premenopausal and postmenopausal women in Japanese (Yamada et al. 2001) and Korean populations (Lee, Lee, et al. 2009). By developing separate prediction models in men and women, the particular men- or women-specific determinants could be found, enhancing the hsCRP predictive ability. Future studies are needed to further examine the biological mechanisms that explain sex differences regarding lifestyle factors and inflammation.

We found that the predicted hsCRP score were positively associated with colorectal adenoma among women who were premenopausal, under fifty years old, and whose educational levels were university or above. Our findings are consistent with previous studies that examined the association between BMI and colorectal status by age and menopausal status (Terry et al. 2001; Adams et al. 2007; Terry, Miller, and Rohan 2002; Hou et al. 2006). Those studies found positive associations between BMI and colorectal cancer only among young women (Terry et al. 2001; Adams et al. 2007) or among premenopausal women (Terry, Miller, and Rohan 2002). A Chinese case-control study reported increasing prevalence of colorectal cancer with increasing BMI among premenopausal women, but decreasing prevalence of colorectal cancer with increasing BMI among postmenopausal women, suggesting that menopausal status may be an important effect modifier for colorectal cancer development. (Hou et al. 2006). In our study, the proportion of women who were fifty years old or above was 91.4% among postmenopausal women and 75% among women whose educational levels were high school or below. It remains unclear whether either age, menopausal status or educational level directly modifies the association between the predicted hsCRP score and colorectal adenoma among women. This warrants further studies.

We observed that the predicted hsCRP score was more strongly associated with increased prevalence of advanced adenoma than non-advanced adenoma. The findings of our strong association in advanced adenoma were similar to previous studies. A meta-analysis showed that circulating levels of CRP were significantly

associated with occurrence of advanced adenoma (OR: 1.59, 95% CI: 1.09, 2.32) (Godos et al. 2017). Most inflammatory cells are recruited after the tumor is formed (Terzic et al. 2010). In this case, inflammation is induced and provoked by a neoplastic lesion. Severe inflammation may facilitate preneoplastic responses, especially advanced neoplasia (Godos et al. 2017). When stratified by anatomical sites, the association were statistically significant for distal colon adenoma among men and for proximal colon adenomas among women. The findings of association between CRP and adenomas stratified by colon and rectum were inconsistent. (Tsilidis et al. 2008; Otake et al. 2009; Song et al. 2016). Two studies reported that the magnitude of the association was higher for distal colon adenoma than other sites (Tsilidis et al. 2008; Otake et al. 2009). In the U.S. nested case-control studies that included only women, the association was statistically significant and the magnitude was higher for proximal colon adenoma than for distal colon and rectal adenoma (Song et al. 2016).

A strength of our study is that 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 further included more than 1,700 Korean participants who underwent colonoscopies, resulting in accurate ascertainment of adenoma cases. Our study also had several limitations. We had relatively few rectal and advanced adenoma cases especially in women. We cannot rule out unmeasured or residual confounding factors. Also, measurement error in dietary assessments may exist.

In conclusion, we developed a prediction model for inflammatory status and found that increasing levels of predicted hsCRP were associated with increasing prevalence of colorectal adenoma in both men and women. The associations were more pronounced for advanced adenoma and the magnitudes of associations were modified by age or menopausal status among women.

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국문초록

고감도C반응단백 예측모델 개발 및 대장선종과의 연관성

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김 세 진

만성염증은 종양의 성장 및 진행에 기여하는 것으로 제안되어 왔다. 메타분석 결과 만성 염증의 지표 역할을 하는 C-반응성 단백질 (C reactive protein, CRP) 의 수치가 증가하면, 대장암 발생률과 대장선종 오즈비가 증가하는 것이 보고되었다. 본 연구에서는 한국 성인을 대상으로 만성염증의 지표인 고감도C반응단백 (high sensitivity C-reactive protein, hsCRP) 의 수치를 예측하는 모델을 개발하고자 하였다. Health Examinee 연구에서 hsCRP 수치 예측모델을 개발하고, 타집단인 대장선종연구에서 모델을 적용하여 예측된 hsCRP 수치와 대장선종과의 연관성을 조사했다. 연구 참여자 (남성 11,665명, 여성

11,665명) 는 무작위로 두 세트로 나누었다: 70%는 모델을 개발하는 training set으로, 30%는 모델을 적용하여 타당도를 확인하는 testing set으로 나뉘었다. 종속변수로 로그 변환된 hsCRP를 두고, 독립변수로 음식, 영양소, 생활습관 관련 요인을 고려하여 단계적 회귀분석을 통해 예측모델을 개발하였다. hsCRP 수치를 예측하는 총 4가지의 버전을 개발하였다: 1) 식품, 2) 식품 및 영양소, 3) 식품 및 생활습관 요인, 4) 식품, 영양소, 생활습관 요인이 고려되었다. Testing set는 예측된 hsCRP 수치의 타당도를 평가하는데 활용되었다. 일반화 선형 모델을 활용하여 예측된 hsCRP 수치에 따른 실제 hsCRP 수치의 상대적 농도를 계산했다. 성별에 따라 CRP 수치와 결정요인이 다를 수 있으므로 남성과 여성을 포함한 집단과 남성과 여성 각각의 집단으로 나누어 모델을 개발하여 타당도와 구성요소를 비교하였다. 이후, 대장선종연구에서 예측된 hsCRP 수치와 대장선종과의 연관성을 검증하였다 (남성 1,056명, 여성 655명). 실제 hsCRP 수치 및 예측된 hsCRP 수치와 대장선종과의 연관성을 확인하기 위해 로지스틱 회귀분석을 사용하여 오즈비 (Odds ratios, ORs) 와 95% 신뢰구간 (Confidence intervals, CIs) 을 계산하였다. 예측된 hsCRP 수치는 남성과 여성에서 모두 실제 hsCRP 수치와 상관관계가 있었다. HEXA 연구에서 예측된 hsCRP 수치가 가장 높은 사분위수 집단의 수치가

가장 낮은 사분위수 집단에 대한 실제 hsCRP 수치의 상대농도는 다음과 같다: 남성에서는 1.65 (95% CI: 1.49, 1.84; p for trend <0.001) 여성에서는 2.02 (95% CI: 1.74, 2.34; p for trend <0.001) 였다. 또한, 실제 hsCRP 수치와 예측된 hsCRP 수치가 증가할수록 남녀 모두 대장선종의 유병률이 증가하였다. 예측된 hsCRP 수치가 가장 높은 사분위수 집단은 수치가 가장 낮은 집단에 비해 대장선종의 유병률이 남성은 1.71배 (95% CI: 1.12, 2.62; p for trend = 0.011) 높았고, 여성은 2.86배 (95% CI: 1.26, 6.49; p for trend = 0.019) 높았다. 잠재적 상호작용 변수에 따라 층화하여 분석한 결과, 50세 미만인 여성이 50세 이상인 여성보다 연관성이 더욱 뚜렷했다. 50세 미만인 여성의 경우, 중위수 이상인 집단이 중위수 미만인 집단에 비해 대장선종의 유병률이 3.74배 (95% CI: 1.77, 7.90) 높았고, 50세 미만인 여성에서는 유의한 연관성이 발견되지 않았으며 (1.09, 95% CI: 0.57, 2.07), 유의한 상호작용 효과가 관찰되었다 (p for interaction = 0.014). 또한, 예측된 hsCRP 수치와 대장선종과의 유의한 연관성은 교육수준이 높거나 폐경 전인 여성에서만 관찰되었다. 또한 양의 연관성은 남성의 경우 원위 결장/직장에서, 여성의 경우 근위 결장에서만 발견되었다. 진행 병기의 경우, 예측된 hsCRP 수치가 중앙값보다 높거나 같은 집단이 낮은 집단에 비해 진행성 대장선종의 유병률이 남성은 1.62배

(95% CI: 1.00, 2.63), 여성은 6.55배 (95% CI: 1.62, 26.37) 로 남녀 모두 진행선종에서 더 높은 연관성이 나타났다. 본 연구에서는 낮은 염증 수치와 연관이 있는 식사 및 생활습관 요인이 대장종양의 질병부담을 낮추는 중요한 전략으로 활용될 수 있다는 점에서 의의가 있다.

주요어: 염증, 고감도C반응단백 (hsCRP), 예측 모델, 예측된 hsCRP 수치, 대장선종

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