Patients with IBD have an increased risk of CRC, and laboratory animals with continuous inflammatory conditions are predisposed to CRC development. Several studies have shown a reduced occurrence of CRC with aspirin or NSAID use. CRP, a widely used marker of inflammation, could be used as a marker to identify individuals at risk for developing CRC. Although a positive correlation between serum CRP level and risk of colorectal neoplasia has been demonstrated, several subsequent studies have shown inconsistent results. The discrepancies between previous studies might be influenced by ethnic population and sex effects. Furthermore, little is known about the association between serum CRP level and risk of colorectal adenoma, a precursor lesion of CRC. Chiu et al. showed a positive association between serum CRP level and risk of colorectal neoplasia in both men and women. Our data may support the association between chronic inflammation and colorectal neoplasia, which warrants further investigation.
Chinese men, but not women. The association of CRP with colorectal adenoma remains undetermined, and further studies on this issue are warranted. The aim of this study was to assess the association between serum CRP and risk of colorectal adenoma.

METHODS

1. Study Population

We conducted a retrospective cross-sectional study on consecutive asymptomatic subjects who underwent a screening colonoscopy as part of a regular medical check-up at the Health Promotion Center of Kyung Hee University Hospital in Gangdong, Seoul, Korea between September 2006 and September 2009. From this colonoscopy database, subjects were retrospectively identified as eligible if they were asymptomatic, had undergone a first-time screening colonoscopy, and had their serum CRP level measured during a routine health check-up. We divided the participants into 2 groups: the high-risk adenoma (HRA) group and the low-risk adenoma (LRA) group. Serum CRP levels were compared between these 2 groups. Potential subjects were excluded if they met any of the following criteria: (1) age younger than 30 years or older than 75 years; (2) any previous colorectal examinations, including colonoscopy, sigmoidoscopy, or barium enema; (3) incomplete colonoscopy because of poor bowel preparation or cecal intubation failure; (4) suspicious clinical infection or fever (temperature >37°C), and (5) history of CRC, rheumatoid arthritis, IBD, coronary artery disease, cerebrovascular accident, or colorectal surgery. Subjects with a history of regular NSAID or aspirin use for >1 year were also excluded due to the potential protective effects of these medications. This study was approved by the Institutional Review Board of our hospital (KHNMC IRB-2015-08-002) and waived for informed consent.

2. Definitions and Exposure Measurements

Before colonoscopy, each subject was questioned by a trained nurse about smoking, alcohol consumption, and medication (NSAID or aspirin) history. Current smoking was defined as at least 1 pack per week for 1 year or longer, and alcohol consumption was defined as drinking more than 140 g of alcohol per week. Regular medication use was defined as the use of medication for more than 12 months. Height and body mass, used to calculate BMI, were routinely measured by trained nurses. Serum CRP was measured by an immunoturbidimetric method using an automatic chemistry analyzer (H7600-1102; Hitachi, Tokyo, Japan). Serum CRP levels were expressed as milligrams per deciliter (mg/dL). The high CRP group was defined as the third and highest quartiles of serum CRP level and the low CRP group was defined as the second and lowest quartiles of serum CRP level.

3. Colonoscopy

Each colonoscopy was performed by an experienced gastroenterologist using a standard colonoscope (EC-590ZW/L; Fujinon Inc., Saitama, Japan); the gastroenterologists were blinded to the patient's serum CRP level. Most colonoscopies were performed under conscious sedation. The bowel preparation agents used were predominantly polyethylene glycol-based, with a split-dose regimen. During the colonoscopy, all detected polyps were completely removed and documented with regard to number, location, and size; all polyps were sent for pathological diagnosis. The pathology reports included the histologic type and grade of dysplasia of each specimen. According to the United States guidelines, LRAs were defined as 1 to 2 tubular adenomas <10 mm, and HRAs were defined as adenomas with villous histology, high-grade dysplasia, ≥10 mm size, or 3 or more adenomas.

4. Statistical Analyses

Student t-tests or Mann-Whitney U-tests were used to compare means, and chi-square tests or Fisher exact tests were used to compare proportions. OR and 95% CI were calculated using logistic regression analysis. All P-values were two-tailed. A P-value <0.05 was considered statistically significant, and P-values <0.1 were considered to indicate a statistical trend. Statistical analyses were performed using the SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 3,603 asymptomatic subjects underwent colonoscopy as part of a regular medical examination, and 147 subjects were excluded from the first-time screening colonoscopy database based on the following criteria: previous colonoscopy (n=69); history of CRC, IBD, or colorectal surgery (n=5); and age younger than 30 or older than 75 years (n=73). An additional 148 patients were excluded from analysis for either failing to complete the study (n=41) or having missing serum CRP or insufficient
data (n=107). Ultimately, 3,309 patients were eligible for this study and were divided into either the HRA group (n=206, 6.2%) or the LRA group (n=3,103, 93.8%). The study population included 1,985 men (60.0%) and 1,324 women (40.0%), with a mean age of 52.4±10.0 years. The prevalence of adenoma in the study population was 24.3%.

1. Baseline Characteristics of the Study Population

The baseline characteristics of the study population in the HRA and LRA groups are shown in Table 1. As expected, patients with HRA were older and more likely to be male compared to those with LRA. In addition, there were a greater number of obese subjects, alcoholics, and smokers in the HRA group than were in the LRA group. Furthermore, the third and highest quartiles of serum CRP level were more common in the HRA group than in the LRA group (P=0.000).

Baseline clinical and pathologic characteristics of the study population according to serum CRP level are summarized in Table 2. The high CRP group had more elderly subjects, males, obese subjects, diabetes patients, aspirin/NSAID users, alcoholics, and smokers than did the control group. In addition, patients with an HRA were more frequently identified in the high CRP group than were identified in the low CRP group (8.6% vs. 4.0%, P<0.001).

2. Associations between Serum CRP and HRA

The associations between serum CRP level and prevalence of HRA are shown in Table 3. The prevalence of HRA was significantly increased according to the serum CRP level quartile. Compared with the lowest quartile of serum CRP level, the prevalence of HRA was 1.2 times higher in the second quartile, 1.8 times higher in the third quartile (P=0.002), and 3.5 times higher in the fourth quartile (P=0.000). Similar associations were observed in both men and women.

To determine independent predictors of the presence of HRA, logistic regression analysis was performed after adjustment for age, sex, BMI, presence of diabetes mellitus, aspirin/

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**Table 1. Baseline Clinical and Laboratory Characteristics of the Study Population According to Risk Group**

|                        | HRA group (n=206) | LRA group (n=3,103) | P-value |
|------------------------|-------------------|--------------------|---------|
| **Clinical characteristics** |                   |                    |         |
| Age (yr)               | 59.4±8.3          | 51.9±9.9           | <0.001  |
| Male sex               | 171 (83.0)        | 1,814 (58.5)       | <0.001  |
| BMI (kg/m²)            | 24.6±2.9          | 23.8±3.1           | <0.001  |
| Diabetes mellitus      | 13 (6.3)          | 148 (4.8)          | 0.322   |
| Aspirin/NSAID use      | 8 (3.9)           | 138 (4.4)          | 0.699   |
| Alcohol consumption    | 95 (46.1)         | 932 (30.0)         | <0.001  |
| Smoking                | 88 (42.7)         | 833 (26.8)         | <0.001  |
| Family history of CRC  | 9 (4.4)           | 103 (3.3)          | 0.419   |
| Bowel preparation (adequate) | 198 (96.1)   | 3,000 (96.7)       | 0.767   |
| **Laboratory characteristics** |                 |                    |         |
| Quartiles of serum CRP (mg/dL) | 0.000           |                    |         |
| Lowest (0.00–0.03)     | 25 (12.2)         | 860 (27.7)         |         |
| Second (0.04–0.06)     | 42 (20.5)         | 762 (24.6)         |         |
| Third (0.07–0.12)      | 62 (30.1)         | 716 (23.1)         |         |
| Highest (0.13–23.6)    | 77 (37.6)         | 765 (24.7)         |         |

Values are presented as mean±SD or number (%). HRA, high-risk adenoma; LRA, low-risk adenoma; CRC, colorectal cancer.

**Table 2. Baseline Clinical and Pathologic Characteristics of the Study Population According to Serum CRP Level**

|                                    | High CRP group (n=1,620)* | Low CRP group (n=1,689)* | P-value |
|------------------------------------|---------------------------|--------------------------|---------|
| **Clinical characteristics**       |                           |                          |         |
| Age (yr)                           | 53.4±10.1                 | 51.4±9.7                 | <0.001  |
| Male sex                           | 1,116 (68.9)              | 869 (51.5)               | <0.001  |
| BMI (kg/m²)                        | 24.7±3.2                  | 23.1±2.9                 | <0.001  |
| Diabetes mellitus                  | 95 (5.9)                  | 66 (3.9)                 | 0.009   |
| Aspirin/NSAID use                  | 84 (5.2)                  | 62 (3.7)                 | 0.033   |
| Alcohol consumption                | 593 (36.6)                | 434 (25.7)               | <0.001  |
| Smoking                            | 557 (34.4)                | 364 (21.6)               | <0.001  |
| Family history of CRC              | 52 (3.2)                  | 60 (3.6)                 | 0.596   |
| Bowel preparation (adequate)       | 1,558 (96.2)              | 1,640 (97.1)             | 0.994   |
| **Pathologic characteristics**     |                           |                          |         |
| High-risk adenoma                  | 139 (8.6)                 | 67 (4.0)                 | <0.001  |
| Any adenoma                        | 447 (27.6)                | 358 (21.2)               | <0.001  |
| Location (proximal)                | 221 (13.6)                | 174 (10.3)               | 0.789   |
| Number                             | 18±1.7                    | 15±1.2                   | 0.015   |
| Size (mm)                          | 5.8±3.9                   | 5.4±3.7                  | 0.165   |
| Histology (TVA/VA)                 | 34 (2.1)                  | 16 (0.9)                 | <0.001  |
| Dysplasia (high-grade)             | 25 (1.5)                  | 18 (1.1)                 | 0.730   |

Values are presented as mean±SD or number (%). The high CRP group was defined as the third and highest quartiles of serum CRP level and the low CRP group was defined as the second and lowest quartiles of serum CRP level. CRC, colorectal cancer; TVA/VA, tubulovillous adenoma/villous adenoma.
Table 3. The Associations between Serum CRP and High-Risk Adenoma in Both Sexes

| Quartiles of serum CRP | OR (95% CI) | P-value |
|------------------------|-------------|---------|
| Male and female combined |             |         |
| Lowest (0.00–0.03 mg/dL) | 1 | - |
| Second (0.04–0.06 mg/dL) | 1.2 (0.8–1.7) | 0.352 |
| Third (0.07–0.12 mg/dL) | 1.8 (1.3–2.7) | 0.002 |
| Highest (0.13–23.60 mg/dL) | 3.5 (2.2–5.5) | 0.000 |
| Male |             |         |
| Lowest (0.00–0.03 mg/dL) | 1 | - |
| Second (0.04–0.06 mg/dL) | 1.1 (0.8–1.7) | 0.559 |
| Third (0.07–0.12 mg/dL) | 1.4 (0.9–2.2) | 0.091 |
| Highest (0.13–23.60 mg/dL) | 2.5 (1.1–4.1) | 0.001 |
| Female |             |         |
| Lowest (0.00–0.03 mg/dL) | 1 | - |
| Second (0.04–0.06 mg/dL) | 1.0 (0.4–2.3) | 0.971 |
| Third (0.07–0.12 mg/dL) | 2.6 (0.9–7.3) | 0.065 |
| Highest (0.13–23.60 mg/dL) | 3.8 (1.3–10.5) | 0.011 |

Table 4. Multivariate Logistic Regression Analysis of Variables for High-Risk Adenoma

| Parameter | OR (95% CI) | P-value |
|-----------|-------------|---------|
| Age (continuous) | 1.1 (1.1–1.1) | 0.000 |
| Sex (male vs. female) | 0.4 (0.3–0.7) | 0.000 |
| BMI (<25 kg/m² vs. ≥25 kg/m²) | 1.2 (0.9–1.7) | 0.148 |
| Diabetes mellitus (no vs. yes) | 0.7 (0.4–1.3) | 0.246 |
| Aspirin/NSAID use (no vs. yes) | 0.4 (0.2–0.9) | 0.027 |
| Alcohol consumption (no vs. yes) | 1.5 (1.1–2.1) | 0.017 |
| Smoking (no vs. yes) | 1.7 (1.2–2.3) | 0.002 |
| Serum CRP (lowest/2nd quartile vs. 3rd/highest quartile) | 1.8 (1.3–2.5) | 0.000 |

Logistic method=enter.

*High-risk adenoma included all cases of adenomas with villous histology, high-grade dysplasia, ≥10 mm, or 3 or more adenomas.

NSAID use, alcohol consumption, smoking, and serum CRP (Table 4). In this analysis, a higher CRP quartile was identified as an independent risk factor for HRA (OR, 1.8; 95% CI, 1.3–2.5; P=0.000).

**DISCUSSION**

Here, we present an association between CRP level and HRA. Compared with the lowest quartile of serum CRP level, the prevalence of HRA was 3.5 times higher in the highest quartile, and HRA was associated with an elevated CRP level in both men and women. In a logistic regression analysis, a higher quartile of CRP was found to be an independent risk factor for HRA (OR, 1.8; 95% CI, 1.3–2.5; P=0.000). Our results support a role of chronic inflammation in the development of colorectal neoplasia. Previous studies have primarily focused on CRC; however, our study focused on HRA, which may be an intermediate lesion in the adenoma-carcinoma sequence. Although some previous studies have suggested sex differences in the association between CRP and colorectal neoplasia, no significant differences were observed in this study.

The role of chronic inflammation in colorectal carcinogenesis has been well established in IBD patients, and a number of studies have also demonstrated an association between CRP level and CRC risk. A recent meta-analysis found a positive association between CRP level and CRC risk. Due to the inconsistencies in previous results, little was conclusively known about the relationship between CRP and colorectal adenoma. In a Japanese case-control study, Otake et al. reported a positive association between CRP and prevalence of large adenomas. The multivariate-adjusted ORs of large adenomas for the lowest to highest quartiles of CRP were 1.00 (reference), 1.81, 1.61, and 2.21, respectively (P=0.01). However, that study was limited due to a lack of information on the use of aspirin or NSAIDs and the nonuniversal definition of large (≥5 mm) adenomas. In a Chinese study, high serum CRP level was independently associated with increased risk of synchronous and advanced colorectal adenomas in Chinese men, but not women. These data supported an association between chronic inflammation and colorectal neoplasia, and suggested an effect of sex on this association. In a small (n=242), colonoscopy-based cross-sectional study, the prevalence of colorectal adenomas was associated with a higher CRP level. Our positive association between CRP level and HRA risk might have been due to the large sample size and use of HRA as a target, as this might indicate an advanced phenotype of colorectal adenoma toward CRC.

Positive associations between CRP and adenoma have not been consistently observed in previous studies. In a small case-control study, serum CRP was not associated with increased risk of colorectal adenoma; however, that study was limited, as only 135 adenoma cases were analyzed. In a case-control study from Korea, serum CRP was not significantly different between normal and adenoma groups. In that study, CRP levels were classified as <1 mg/dL, 1 to 3 mg/dL, >3 mg/dL; however, this classification was arbitrary and included very high levels, considering the relatively healthy...
population. In our study, the mean CRP level was 0.2±0.9 mg/dL, and only 2.4% of the study population had CRP >1 mg/dL. CRP may be associated with increased risk of adenoma at very low levels, and this positive association might be obscured by arbitrary classifications of CRP levels. Recently, a prospective colorectal adenoma chemoprevention study found no significant relationship between CRP level and recurrent adenoma or advanced neoplasm. However, this was a chemoprevention study with calcium supplementation (1,200 mg/day), which might have influenced the levels of CRP, and recurrent adenoma was evaluated only 3 years after baseline CRP levels were measured, which could have been too short of a duration to evaluate the recurrence of adenoma. In another prospective case-control study, high CRP level was protective effect against colorectal adenoma development; however, that study was also limited by a sigmoidoscopy-based study design with small sample size. These inconsistent previous results might have arisen from different study methodologies, patient populations, and prevalence of colorectal neoplasia.

The mechanism involved in the association between CRP level and colorectal neoplasia is currently unknown. Further studies on this subject are required; however, there are several possible explanations. As patients with obesity, smoking, physical inactivity, and diabetes mellitus have high CRP levels, we infer that these factors jointly contribute to the increased risk for HRA. However, even after adjustment for these confounding factors, CRP remained an independent risk factor for colorectal neoplasia. Another possible explanation is that CRP level might be associated with insulin resistance, which is a shared pathway for the development of colorectal neoplasia. These results may suggest that the association between CRP and colorectal neoplasia is not a coincidence but rather the result of a common pathway.

There are several advantages to our study. First, this is the first study to explore the association between CRP and presence of HRA. As the prevalence of HRA, which must be evaluated with invasive colonoscopy and pathologic examination, has been increasing, a laboratory marker for identifying HRA and related mechanisms warrants further investigation.

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