ORIGINAL ARTICLE

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2017.15.4.511
Intest Res 2017;15(4):511-517

High C-reactive protein level is associated with high-risk adenoma

Hyae Min Lee, Jae Myung Cha, Jung Lok Lee, Jung Won Jeon, Hyun Phil Shin, Kwang Ro Joo, Jin Young Yoon, Joung Il Lee

Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea

Background/Aims: There is substantial evidence supporting a role of inflammation in the pathogenesis of colorectal cancer; however, little is known about the association between serum C-reactive protein (CRP) and the risk of colorectal adenoma. This study was conducted to investigate the association between serum CRP and colorectal adenoma risk. **Methods:** A retrospective cross-sectional study was performed on first-time screening colonoscopies in asymptomatic subjects who also had their serum CRP level measured during a routine health check-up between September 2006 and September 2009 in Korea. Serum CRP level was compared between high-risk and low-risk adenoma groups and independent predictors of high-risk adenoma were analyzed using multivariate regression analysis. **Results:** Among the 3,309 eligible patients, the high-risk adenoma group had higher serum CRP levels than the low-risk adenoma group (P=0.000). In addition, patients with a high-risk adenoma were more frequently included in the high CRP group than in the low CRP group (8.6% vs. 4.0%, P<0.001). The prevalence of high-risk adenoma was 3.5 times higher in the highest quartile of CRP level (P=0.000) compared with that in the lowest quartile. In logistic regression analysis, a higher quartile CRP level was found to be an independent risk factor for high-risk adenoma (odds ratio, 1.8; 95% confidence interval, 1.3–2.5; P=0.000). **Conclusions:** High CRP level is associated with high-risk adenoma in both men and women. Our data may support the association between chronic inflammation and colorectal neoplasia, which warrants further investigation. **(Intest Res 2017;15:511-517)**

Key Words: Colon; Inflammation; Neoplasms; C-reactive protein; Colonoscopy

INTRODUCTION

Colorectal cancer (CRC) is an important public health concern, and its incidence has been increasing worldwide.[1,2] As most CRCs develop from colorectal adenomas through the adenoma-carcinoma sequence, CRC screening can decrease CRC-related mortality through early detection and removal of colorectal adenomas.[3,4] Growing evidence supports a role of inflammation in the pathogenesis of CRC.[5-13] Patients with IBD have an increased risk of CRC,[5] and laboratory animals with continuous inflammatory conditions are predisposed to CRC development.[6] Several studies have shown a reduced occurrence of CRC with aspirin or NSAID use.[7-13]

CRP, a widely used maker of inflammation, could be used as a marker to identify individuals at risk for developing CRC.[14] Although a positive correlation between serum CRP level and risk of colorectal neoplasia has been demonstrated,[15-19] several subsequent studies have shown inconsistent results.[20-23] 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.[17] showed a positive association between serum CRP level and risk of colorectal neoplasia in

Received April 14, 2016. **Revised** June 28, 2016.
Accepted July 3, 2016. **Published online** May 18, 2017
Correspondence to Jae Myung Cha, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea. Tel: +82-2-440-6113, Fax: +82-2-440-6295, E-mail: drcha@khu.ac.kr

Financial support: None. **Conflict of interest:** None.

© Copyright 2017. Korean Association for the Study of Intestinal Diseases. All rights reserved.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 a 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,[24] 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

https://doi.org/10.5217/ir.2017.15.4.511 • Intest Res 2017;15(4):511-517

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).

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/m^2)	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.

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/

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

	High CRP group (n=1,620)[a]	Low CRP group (n=1,689)[a]	*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/m^2)	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	1.8±1.7	1.5±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 (%).
[a]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[a]

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/m^2 vs. ≥25 kg/m^2)	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.
[a]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 of HRAs (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,[17,25] no sex differences were observed in this study.

The role of chronic inflammation in colorectal carcinogenesis has been well established in IBD patients,[5] and a number of studies have also demonstrated an association between CRP level and CRC risk.[15,16,19] A recent meta-analysis found a positive association between CRP level and CRC risk.[14] Due to the inconsistencies in previous results,[17,20-22,26-28] little was conclusively known about the relationship between CRP and colorectal adenoma. In a Japanese case-control study, Otake et al.[26] 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,[17] high serum CRP level was independently associated with increased risk of synchronous and advanced colorectal neoplasia 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.[27] 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.[20-23] 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.[23] In a case-control study from Korea, serum CRP was not significantly different between normal and adenoma groups.[22] 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.[20] 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,[21] 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,[29] smoking,[30] physical inactivity,[31] and diabetes mellitus[32] 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,[17] CRP remained an independent risk factor for colorectal neoplasia. Another possible explanation is that CRP level might be associated with insulin resistance,[32-34] which is a shared pathway for the development of colorectal neoplasia.[32,35] 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 HRA would be clinically useful. Second, we included many potential confounding factors that can influence CRP level, such as BMI, diabetes mellitus, aspirin/NSAID use, alcohol consumption, and smoking. However, we cannot exclude the possibility of residual confounding factors. Finally, the data collected in this study are of high quality, despite the retrospective design of this study, because the questionnaires were completed by trained nurses, and the adenoma detection rate (24.3%) of this study was matched to quality indicators of colonoscopy.

Despite these advantages, there are also several limitations to our study. First, our study used only a single measurement of CRP at baseline before colonoscopy. However, single measurements of baseline CRP have strongly predicted risk for diabetes mellitus,[32] coronary heart disease,[36] and hypertension[37] in other studies. Furthermore, CRP level is stable over long periods,[38] with little or no diurnal variation.[39] Second, we measured CRP level before colonoscopy without a subsequent measurement after removal of the colonic neoplasia, preventing us from concluding a causal relationship. Third, our results are based on a single-center retrospective study, which limits the generalization of our findings. Finally, we cannot exclude the possibility that a high CRP level is an epiphenomenon of a systemic infectious state. However, this possibility is remote, as only asymptomatic individuals were included and individuals with a suspicious clinical infection or fever were excluded. Furthermore, the proportion of patients with CRP ≥5 mg/dL was only 0.4% and with CRP ≥10 mg/dL was only 0.2%.

In conclusion, our study showed that high CRP level is associated with HRA in both men and women. The feasibility of using CRP as a laboratory marker for identifying HRA and related mechanisms warrants further investigation.

REFERENCES

1. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res Treat 2013;45:1-14.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Burt RW. Colorectal cancer screening. Curr Opin Gastroenterol 2010;26:466-470.
4. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy: the National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981.
5. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004;287:G7-G17.
6. Maggio-Price L, Treuting P, Zeng W, Tsang M, Bielefeldt-Ohmann H, Iritani BM. Helicobacter infection is required for inflammation and colon cancer in SMAD3-deficient mice. Cancer Res 2006;66:828-838.

7. Sansbury LB, Millikan RC, Schroeder JC, Moorman PG, North KE, Sandler RS. Use of nonsteroidal antiinflammatory drugs and risk of colon cancer in a population-based, case-control study of African Americans and Whites. Am J Epidemiol 2005;162:548-558.
8. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891-899.
9. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883-890.
10. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313-1316.
11. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 1991;101:635-639.
12. Ladenheim J, Garcia G, Titzer D, et al. Effect of sulindac on sporadic colonic polyps. Gastroenterology 1995;108:1083-1087.
13. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946-1952.
14. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA. C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. Int J Cancer 2008;123:1133-1140.
15. Wu J, Cai Q, Li H, et al. Circulating C-reactive protein and colorectal cancer risk: a report from the Shanghai Men's Health Study. Carcinogenesis 2013;34:2799-2803.
16. Toriola AT, Cheng TY, Neuhouser ML, et al. Biomarkers of inflammation are associated with colorectal cancer risk in women but are not suitable as early detection markers. Int J Cancer 2013;132:2648-2658.
17. Chiu HM, Lin JT, Chen TH, et al. Elevation of C-reactive protein level is associated with synchronous and advanced colorectal neoplasm in men. Am J Gastroenterol 2008;103:2317-2325.
18. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004;291:585-590.
19. Rhodes JM, Campbell BJ. Inflammation and colorectal cancer: IBD-associated and sporadic cancer compared. Trends Mol Med 2002;8:10-16.
20. Crockett SD, Mott LA, Barry EL, et al. C-reactive protein and risk of colorectal adenomas or serrated polyps: a prospective study. Cancer Prev Res (Phila) 2014;7:1122-1127.
21. Gunter MJ, Cross AJ, Huang WY, et al. A prospective evaluation of C-reactive protein levels and colorectal adenoma development. Cancer Epidemiol Biomarkers Prev 2011;20:537-544.
22. Park SK, Park DI, Park JH, et al. C-reactive protein level and colorectal adenoma. Korean J Gastroenterol 2008;51:225-231.
23. Ito Y, Suzuki K, Tamakoshi K, et al. Colorectal cancer and serum C-reactive protein levels: a case-control study nested in the JACC Study. J Epidemiol 2005;15 Suppl 2:S185-S189.
24. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on colorectal cancer. Gastroenterology 2012;143:844-857.
25. Rogowski O, Zeltser D, Shapira I, et al. Gender difference in C-reactive protein concentrations in individuals with atherothrombotic risk factors and apparently healthy ones. Biomarkers 2004;9:85-92.
26. Otake T, Uezono K, Takahashi R, et al. C-reactive protein and colorectal adenomas: Self Defense Forces Health Study. Cancer Sci 2009;100:709-714.
27. Kim S, Keku TO, Martin C, et al. Circulating levels of inflammatory cytokines and risk of colorectal adenomas. Cancer Res 2008;68:323-328.
28. Tsilidis KK, Erlinger TP, Rifai N, et al. C-reactive protein and colorectal adenoma in the CLUE II cohort. Cancer Causes Control 2008;19:559-567.
29. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911-919.
30. Kawada T. Relationships between the smoking status and plasma fibrinogen, white blood cell count and serum C-reactive protein in Japanese workers. Diabetes Metab Syndr 2015;9:180-182.
31. Longo-Mbenza B, Nkongo Mvindu H, Kasiam On'kin JB, et al. The deleterious effects of physical inactivity on elements of insulin resistance and metabolic syndrome in Central Africans at high cardiovascular risk. Diabetes Metab Syndr 2011;5:1-6.
32. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327-334.
33. Effoe VS, Correa A, Chen H, Lacy ME, Bertoni AG. High-sensitivity C-reactive protein is associated with incident type 2 diabetes among African Americans: the Jackson Heart Study. Diabetes Care 2015;38:1694-1700.
34. Rampal S, Yang MH, Sung J, et al. Association between markers of glucose metabolism and risk of colorectal adenoma. Gastroenterology 2014;147:78-87.e3.
35. Kang HW, Kim D, Kim HJ, et al. Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. Am J Gastroenterol 2010;105:178-187.

36. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-1565.
37. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. JAMA 2003;290:2945-2951.
38. Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek E. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. Clin Chem 2001;47:444-450.
39. Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. Clin Chem 2001;47:426-430.