The association between progression of coronary artery calcium and colorectal adenoma

A retrospective follow-up study of asymptomatic Koreans

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Abstract

The potential relationship between coronary artery calcium (CAC) and colorectal adenoma has been widely indicated. This study aimed to investigate the relationship between the risk of colorectal adenoma and CAC progression in asymptomatic Korean adults who underwent serial assessments by colonoscopy and CAC scan.

A total of 754 asymptomatic participants, who had undergone serial CAC scans and colonoscopies for screening, were enrolled. Changes in CAC were assessed according to the absolute change between baseline and follow-up results. CAC progression was defined using Multi-Ethnic Study of Atherosclerosis method. Risk for adenoma at follow-up colonoscopy was determined using hazard ratio (HR) by Cox regression. The area under the receiver operating characteristic (ROC) curve was measured.

The mean follow-up duration was 3.4 \( \pm \) 2.5 years. CAC progression was found in 215 participants (28.5%). Participants with adenoma at index colonoscopy showed a higher rate of CAC progression than those without (38.8\% vs 23.6\%, \( P < .01 \)). In participants with adenoma at index colonoscopy, CAC progression significantly increased the cumulative risk for adenoma at follow-up colonoscopy (HR = 1.48, 95\% confidence interval [CI] 1.06–2.06, log-rank \( P = .021 \)). In multivariate analysis, male sex (HR = 2.57, 95\% CI 1.22–5.42, \( P = .013 \)), \( \geq 3 \) adenomas at index colonoscopy (HR = 2.60, 95\% CI 1.16–5.85, \( P = .021 \)), and CAC progression (HR = 2.74, 95\% CI 1.48–5.08, \( P = .001 \)) increased the risk of adenoma at follow-up colonoscopy. In participants without adenoma at index colonoscopy, baseline CAC presence nor CAC progression increased the risk of adenoma at follow-up colonoscopy. The interaction between CAC progression and adenoma at index colonoscopy was significant in multivariable model (\( P = .005 \)). In the ROC analysis, AUC of CAC progression for adenoma at follow-up colonoscopy was 0.625 (95\% CI 0.567–0.684, \( P < .001 \)) in participants with adenoma at index colonoscopy.

Participants with CAC progression, who are at high risk of coronary atherosclerosis, may need to be considered for follow-up evaluation of colorectal adenoma, especially those with adenoma at index colonoscopy.

Abbreviations: BMI = body mass index, BP = blood pressure, CAC = coronary artery calcium, CI = confidence interval, CT = computed tomography, HR = hazard ratio, HTN = hypertension, MESA = Multi-Ethnic Study of Atherosclerosis.

Keywords: atherosclerosis, colonoscopy, colorectal neoplasms, coronary artery disease

1. Introduction

Colorectal cancer is a major cause of mortality worldwide.\textsuperscript{[1]} About 85\% of colorectal cancers are considered to develop from colorectal adenoma through a process termed adenoma-to-carcinoma sequence.\textsuperscript{[2]} Therefore, early detection and removal of colorectal adenomas is important to prevent their progression to colon cancer.\textsuperscript{[1,3]} Current guidelines recommend polyp surveillance based on baseline examination and family history of colorectal cancer and high-grade adenomas.\textsuperscript{[6,7]} Presence of adenoma or...
adenoma characteristics at baseline colonoscopy are associated with the rate of the subsequent adenomas during surveillance.[11] Compared with the normal group (no adenoma at baseline), 5-year cumulative rates of overall adenoma showed an increase across the risk groups (adenomas at baseline).[8] Size of adenoma, number of adenoma or adenoma pathological features at baseline have been used for risk stratification. However, in regards to other risk factors, there is insufficient evidence to tailor recommendations. Identification of risk factors for colorectal neoplasia may guide the establishment of strategies targeted towards colorectal cancer prevention.

Cardiovascular disease is also among the most common causes of mortality worldwide, and it has enormously contributed to the economic burdens associated with healthcare costs.[9,10] Coronary artery calcium (CAC) scanning is an established method for assessing the presence of atherosclerotic plaque in the asymptomatic population.[11,12] Current guidelines recommend that CAC scanning should be considered in the risk assessment of cardiovascular disease in asymptomatic populations.[13]

Previous studies have indicated the potential relationship between CAC and colorectal adenoma.[14,15] Colorectal neoplasm and coronary atherosclerosis have common risk factors, such as components of metabolic syndrome, diabetes mellitus, smoking, hyperlipidemia, obesity, and hypertension (HTN).[15–17] However, only cross-sectional studies have been published to date.[13–15] Considering the dynamic nature of CAC progression and colorectal adenoma, a longitudinal analysis of the relationship between CAC progression and colorectal adenoma or prospective study are needed. The present study aimed to investigate whether CAC progression is associated with colorectal adenoma independently of other risk factors such as age, sex, smoking, alcohol, family history of colorectal cancer, body mass index (BMI), advanced adenomas at index colonoscopy, and baseline presence of CAC. Interaction test between CAC progression and adenoma at index colonoscopy was presented for effect modification.

2. Methods

2.1. Study populations

We retrospectively reviewed participants who underwent health screening examinations from July 2006 to November 2017 at a single health promotion center in South Korea. Medical records of 781 consecutive participants, who had undergone serial CAC scans and colonoscopy on the same day during routine health screening, were reviewed. For this analysis, we excluded 27 subjects with a history of colorectal cancer, colon resection, inflammatory bowel diseases (ulcerative colitis or Crohn’s disease), or myocardial infarction, in addition to subjects with a history of previous coronary revascularization. Finally, a total of 754 subjects were enrolled in the current analysis. The average duration between computed tomography (CT) evaluations was 3.4 ± 2.5 years. Written informed consent was obtained from each participant, and the appropriate institutional review board committee approved the study protocol (IRB No. 2018-0188-001).

2.2. Clinical and laboratory data

Participants’ demographics and medical histories were collected retrospectively through review of medical records. Participants demographics, including age, sex, height, weight, BMI, and blood pressure (BP), which were measured at the time of each evaluation, were collected. Past medical history information was collected via self-administered medical questionnaire. Hypertension was defined as a systolic BP of ≥140 mmHg, a diastolic BP of ≥90 mmHg and/or the current use of antihypertensive agents. Participants with diabetes mellitus were defined as those with a fasting plasma glucose level of ≥126 mg/dL, or currently on anti-diabetic medications. Smokers were presented as current smokers and ex-smokers. Laboratory evaluation included measurements of total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting glucose levels. Venous blood samples were collected before 10 AM after 12-hour overnight fasting.

2.3. CAC scanning and colonoscopy

Participants underwent CAC scanning using multi-detector CT (Philips Brilliance 64; Philips Medical Systems, Best, The Netherlands) using 3-mm slice thickness and 1.5-mm reconstruction interval. Participants with heart rates >66 beats/minute were administered beta-blockers (25-mg atenolol; Tenormin, Hyundai, Seoul, Korea) before CT. CAC score was measured using Agatston method.[18] CAC was repeatedly measured using multi-detector CT, and progression of CAC was defined according to Multi-Ethnic Study of Atherosclerosis (MESA) method. For those with CAC = 0 at baseline, progression was defined as CAC score >0 at follow-up; for those with 0 < CAC ≤ 100 at baseline, progression was defined as an annualized change of ≥10 Agatston units at follow-up; and for those with CAC > 100 at baseline, progression was defined as an annualized percent change (annualized change in CAC score divided by the baseline CAC score) of ≥10% at follow-up.[19] Subjects were categorized as having either CAC progression or CAC non-progression.

Colonoscopies were performed by 6 board-certified endoscopists who had performed a minimum of 3000 colonoscopies with a cecal intubation rate of 99%. Examinations were conducted using a standard video colonoscope (CF-H260AI; Olympus, Tokyo, Japan). The interval duration of follow-up colonoscopy was recommended by the endoscopists. The size of adenoma was estimated using biopsy forceps, and in participants with synchronous adenomas, the largest size obtained was subject to statistical analysis. The number of adenomas was calculated from each colonoscopy at every follow-up CT. Advanced adenomas (adenoma ≥1 cm, ≥3 adenomas, and villous or high-grade adenomas) at index colonoscopy were examined. All of the adenomas found during colonoscopy were removed using cold biopsy or standard polypectomy method.

Metachronous adenoma was defined as the presence of any adenomatous polyps during the follow-up colonoscopy performed at >6 months after complete resection of adenoma during index colonoscopy.[20] In this study, follow-up colonoscopy was performed at least 1 year after index colonoscopy.

2.4. Statistical analysis

According to the presence of adenoma at index colonoscopy, CAC progression was compared with other potential variables using independent 2-sample t tests for continuous variables and chi-squared test or Fisher exact test for categorical variables. Continuous variables were expressed as the mean ± standard deviation, whereas categorical variables were presented as the count with proportion. Cox regression analysis was used to determine the hazard ratio (HR) for the likelihood of metachronous adenoma at follow-up colonoscopy according
to relevant variables. Adenomas at follow-up colonoscopy were compared using Kaplan–Meier method, and tested for differences with log-rank test. Cox regression interaction effect was used to analyze effect modifications by interaction tests between CAC progression and adenoma at index colonoscopy. Prediction was assessed using a receiver operating characteristic (ROC) curve and AUC (the area under the curve) was presented. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics of the study population

Baseline characteristics of the 754 participants, in terms of the presence of adenoma at index colonoscopy in comparison to CAC progression by MESA method, are shown in Table 1. Of the 754 participants, 245 (32.5%) had adenoma at index colonoscopy. Of the 245 participants with adenoma at index colonoscopy, 95 (38.8%) participants showed CAC progression at the follow-up CT scan. Of the 509 participants without adenoma at index colonoscopy, 120 (23.8%) participants showed adenoma at follow-up colonoscopy. Of the 245 participants with adenoma at index colonoscopy in comparison to CAC progression by MESA method, are shown in Table 1. Of the presence of adenoma at index colonoscopy in terms of the

Table 1
Baseline characteristics and comparison of baseline characteristics between subjects who CAC progression and non-progression by Multi-Ethnic Study of Atherosclerosis (MESA) method according to presence of adenoma at index colonoscopy.

| Without adenoma | With adenoma |
|-----------------|-------------|
|                 | CAC non-progression | CAC progression | P value | CAC non-progression | CAC progression | P value |
| Age, years      | 50.54±7.59 (n=380) | 54.05±8.17 (n=120) | <.001 | 54.26±7.93 (n=150) | 56.08±7.67 (n=95) | .09 |
| Male sex        | 245 (62.98%) | 104 (86.67%) | <.001 | 110 (73.33%) | 85 (89.47%) | .002 |
| Smoking, current smoker | 18 (4.63%) | 15 (12.50%) | .002 | 18 (12.00%) | 11 (11.58%) | .92 |
| Smoking, ex-smoker | 34 (8.74%) | 18 (15.00%) | .001 | 20 (13.33%) | 22 (23.16%) | .92 |
| Brinkman Index  | 21.7±9.2 | 25.6±9.9 | .001 | 25.4±11.5 | 22.3±9.6 | .001 |
| Alcohol habitual | 70 (17.99%) | 34 (28.33%) | .14 | 45 (30.00%) | 34 (35.79%) | .34 |
| Family history of colorectal cancer | 5 (1.29%) | 5 (4.17%) | .06 | 1 (0.67) | 1 (1.05) | .99 |
| Aspirin         | 15 (3.86%) | 5 (4.17%) | .007 | 10 (6.67) | 11 (1.05) | .18 |
| Body mass index, kg/m² | 23.75±2.37 | 25.08±2.58 | <.001 | 24.21±2.56 | 25.22±3.03 | .006 |
| Systolic blood pressure, mmHg | 121.2±15.91 | 127.9±16.10 | <.001 | 127.4±16.92 | 130.6±16.55 | .23 |
| Diastolic blood pressure, mmHg | 76.02±10.17 | 79.81±10.41 | .0004 | 79.8±10.16 | 80.9±8.81 | .37 |
| Glucose, mg/dL  | 96.02±17.95 | 103.2±22.60 | <.001 | 98.90±18.48 | 102.8±18.04 | .10 |
| Total cholesterol, mg/dL | 195.5±35.53 | 190.6±39.02 | .96 | 194.52±36.38 | 199.8±39.36 | .27 |
| Low-density lipoprotein cholesterol, mg/dL | 122.9±30.57 | 124.0±37.75 | .78 | 122.40±34.15 | 127.8±37.19 | .25 |
| High-density lipoprotein cholesterol, mg/dL | 52.20±13.55 | 45.88±10.47 | <.001 | 48.64±12.24 | 48.51±10.68 | .93 |
| Log-transformed Triglycerides | 2.02±0.22 | 2.10±0.24 | <.001 | 2.08±0.22 | 2.05±0.20 | .88 |
| Hypertension    | 67 (17.22%) | 40 (33.33%) | .0002 | 44 (39.33) | 41 (36.16) | .027 |
| Diabetes mellitus | 102 (26.22%) | 53 (44.17%) | .0002 | 52 (34.67) | 39 (41.05) | .31 |
| Lipid medication | 100 (25.71%) | 51 (42.50%) | .0004 | 51 (34.00) | 30 (31.58) | .69 |
| CAC at baseline, mean | 14.06±8.32 | 53.16±113.5 | .0006 | 55.71±94.3 | 71.8±225.3 | .62 |
| CAC >0 at baseline | 65 (16.71) | 57 (47.50) | <.001 | 46 (30.67) | 56 (58.95) | <.001 |
| Advanced adenoma at index colonoscopy | 33 (22.00%) | 22 (23.16) | .83 |
| Adenoma ≥1 cm | 17 (11.29) | 10 (10.53) | .84 |
| 3 or more adenomas | 28 (16.67) | 14 (14.74) | .42 |
| Villous or high-grade adenoma | 7 (4.67) | 5 (5.26) | .99 |
| 2 or more follow-up of colonoscopy during CAC scan follow-up | 117 (30.08) | 51 (42.50) | .011 | 53 (35.33) | 45 (47.37) | .06 |
| CAC scan follow-up duration | 48.79±25.16 | 55.54±26.68 | .012 | 45.73±22.11 | 47.28±22.04 | .59 |

Data are presented as mean ± SD (standard deviation) or number (%).
CAC=coronary artery calcium.
multivariable models were statistically significant (univariable model, $P=0.014$; multivariable model, $P=0.005$).

In participants with adenoma at index colonoscopy, risk factors for metachronous adenoma at follow-up colonoscopy were male sex ($HR=2.507$, 95% CI $1.225$–$5.421$, $P=0.013$), $\geq 3$ adenomas at the index colonoscopy ($HR=2.336$, 95% CI $1.133$–$4.902$, $P=0.025$), CAC $>0$ at baseline (compared to $CAC=0$) ($HR=2.005$, 95% CI $1.182$–$3.402$, $P=0.01$), and CAC progression ($HR=3.033$, 95% CI $1.736$–$5.299$, $P<0.01$). Multivariable analysis (multivariable model I) showed that the risks of metachronous adenoma were significantly higher in men ($HR=2.495$, 95% CI $1.212$–$5.138$, $P=0.013$) and those with CAC progression ($HR=2.582$, 95% CI $1.405$–$4.746$, $P=0.002$). Multivariable analysis considering adenoma characteristics at index colonoscopy (multivariable model II) showed that male sex ($HR=2.573$, 95% CI $1.223$–$5.421$, $P=0.013$), $\geq 3$ adenomas at index colonoscopy ($HR=2.60$, 95% CI $1.156$–$5.489$, $P=0.021$), and CAC progression ($HR=2.739$, 95% CI $1.478$–$5.077$, $P=0.001$) increased the risks of adenoma.

Kaplan–Meier cumulative event curve for metachronous adenoma at follow-up colonoscopy between CAC progression and CAC non-progression groups is shown in Figure 1. CAC progression increased the risk of adenoma at follow-up colonoscopy in participants with adenoma at index colonoscopy ($HR=1.497$, 95% CI $1.059$–$2.064$, log-rank test $P=0.021$), but not in participants without adenoma at index colonoscopy ($HR=0.932$, 95% CI $0.66$–$1.317$, log-rank test $P=0.69$).

In the ROC analysis, AUC of CAC progression for adenoma at follow-up colonoscopy was 0.625 (95% CI $0.567$–$0.684$, $P<0.001$) in participants with adenoma at index colonoscopy (Fig. 2). CAC progression was not significant in participants without adenoma (AUC=$0.521$, 95% CI $0.481$–$0.561$, $P=0.314$).

4. Discussion

In this study, we investigated the relationship between CAC progression and metachronous colorectal adenoma in a population of asymptomatic healthy Koreans who underwent serial health check-ups. Progression of CAC is associated with metachronous adenoma in participants with adenoma at index colonoscopy, but not in those without adenoma at index colonoscopy. Interaction test between the progression of CAC and adenoma at index colonoscopy was statistically significant after adjusting for other confounders.

Previous studies have indicated potential relationships between CAC and colorectal adenoma. Choi et al showed that the prevalence of advanced adenoma is higher in subjects with severe coronary atherosclerosis. Yun et al reported that colorectal adenoma was more likely to be present in participants with higher CAC. The findings of the present study expand on these previous results by demonstrating serial assessment by CAC scans and colonoscopy. A recent study has indicated that CAC progression is related to incident hard and total coronary heart
disease events in a multiethnic cohort with CAC scans performed an average of 2.5 years apart. The progression of CAC adds a significant incremental predictive value for all-cause mortality after adjusting for time between scans, demographics, risk factors, and baseline CAC score. In addition to previous findings, our results have demonstrated that progression of CAC increased the risk of metachronous adenoma. The threshold of CAC increase or change optimal cut-off point was 17.38 (sensitivity = 37.22 (95% CI 31.8–42.9), specificity = 84.27 (95% CI 80.5–87.5)) (supplementary Figure 1, http://links.lww.com/MD/D297). In all participants, AUC by progression score of CAC for adenoma at follow-up colonoscopy was 0.604 (95% CI 0.568–0.641, P < .001). In ROC analysis, CAC progression was significant in participants with adenoma at index colonoscopy. To our knowledge, this is the first study to reveal the longitudinal relationship between progression of CAC and colorectal adenoma. Given the heterogeneous nature of the development of colorectal adenoma and progression of CAC, serial assessment by CT scans may be helpful to identify participants with high risk of colorectal adenoma at follow-up.

Participants with CAC progression are considered to be at high risk of coronary atherosclerosis. The traditional CAC scores make several assumptions about the biology of calcification and atherosclerosis that warrant discussion. An improved or advanced CAC score will provide an opportunity to reconsider assumptions inherent in traditional CAC scoring. However, CAC has a significant prognostic value across a wide spectrum of age and risk factor profiles. CAC is associated with atherosclerotic burden, and CAC scanning has been proposed as a measure to track coronary heart disease progression and the effects of risk factor modification on atherosclerosis. Despite some debates about the relationship between CAC and atherosclerosis, CAC and its progression are markers of subclinical atherosclerosis. Repeat CAC scanning has been proposed as a method to track progression of total atherosclerosis burden and CAC progression correlates with worsening atherosclerosis.

In previous cross-sectional study, prevalence of colorectal adenoma was greater in subjects with mild or significant CAD and the presence of advanced colorectal adenoma was significantly associated with significant CAD. This study supports previous findings and presented the association between CAC and colorectal adenoma in longitudinal analysis. These are helpful for planning the screening of colorectal neoplasm and coronary atherosclerosis in asymptomatic individuals. But we did
not identify the association between CAC with advanced adenoma at follow-up colonoscopy, the association between progression of CAC and advanced adenoma is needed to clarify in the future.

There are possible explanations for the current relationship between progression of CAC and colorectal adenoma. The progression of CAC and colorectal adenoma may be associated, probably through insulin resistance or inflammation. Several previous studies have reported that metabolic syndrome was a risk factor for colorectal neoplasm and also atherosclerosis.[10,11] Insulin resistance is believed to play a major role in the underlying pathophysiology of metabolic syndrome, possibly contributing to atherosclerosis[12] and colorectal adenoma.[13] Since metabolic syndrome has a positive relationship with colorectal cancer,[14] progression of CAC representing atherosclerosis and adenoma representing colorectal neoplasia may have shared risk factors. The insulin/insulin-like growth factor-1 pathway was suggested by mediating mitogenicity by activation of K-ras, increasing the activity of ras protein occurring in abnormal colonocytes, and stimulating the progression of adenomas into cancers.[15]

Otherwise, several inflammatory biomarkers, such as macrophage inhibitory cytokine 1 or pro-inflammatory cytokine macrophage migration inhibitory factor (MIF)[16–20] and high-sensitivity C-reactive protein (hs-CRP),[21–24] have been associated with increased risks of cardiovascular disease and colorectal cancer. In addition, sub-clinical inflammation induces oxidative stress progresses the development of atherosclerotic lesions and also leads to DNA damage with an increased risk of developing colorectal cancer.[25] CAC progression in participants with adenoma at index colonoscopy may have a higher risk for insulin resistance or inflammation. Given that there was no definitive serologic marker for advanced adenoma or adenoma, finding inflammatory candidates for colorectal neoplasm may be helpful in applying individualized colonoscopy intervals in clinical practice.

There were several limitations to this study. Given the retrospective nature of the current study, predominance of male participants (71.9%), self-referred, and relatively small sample size, the study cohort did not represent the general population. Furthermore, the study may contain selection bias, and confounding factors to infer causal relationships between colorectal adenoma and CAC progression were limited. We did not include inflammatory biomarkers (MIF, TNF-a, IL-6 or hs-CRP) or insulin resistance markers. In this study, any alcohol consumption seemed to lower the risk of adenoma in multivariable models. We did not identify the frequency of alcohol consumption, drinking pattern, and whether participants drank strong alcohol. More information related to alcohol consumption is needed to clarify these findings. CAC scans and colonoscopy evaluation intervals were inconsistent. We did not identify the association between CAC with advanced adenoma at follow-up colonoscopy. However, the longitudinal data showed that participants with CAC progression were at risk of metachronous adenoma at follow-up colonoscopy. The interaction test between CAC progression and adenoma also showed statistical significance in multivariable analysis. By demonstrating the relationship between metachronous colorectal adenoma and CAC progression, serial CAC evaluation in participants who were screened for cardiac disease may be helpful in predicting the risk of colorectal adenoma.

In conclusion, CAC progression is associated with metachronous adenoma at follow-up colonoscopy in participants with adenoma at index colonoscopy. Individuals with CAC progression, who are at high risks of coronary atherosclerosis, may need to be considered for follow-up evaluation of colorectal adenoma, especially those with adenoma at previous colonoscopy. Assessment according to individual risk status is needed for colorectal neoplasm, and this study may help physicians to better understand the relationship between CAC progression and colorectal adenoma. Prospective study and investigation in different ethnic populations and explorations of genetic aspects will help clarify the risks of colorectal neoplasm. Further prospectively designed studies confirming the relationship between CAC progression and colorectal adenoma are warranted.

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