The association between coronary calcification and adenomatous polyp of colon in Korean adults

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The association between coronary calcification and adenomatous polyp of colon in Korean adults

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ABSTRACT

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Background: Colon cancer is one of the most common malignancies and the adenomatous polyp of colon is a precancerous lesion. Screening for colon polyps has been shown to reduce colorectal cancer mortality. Many studies have shown that the adenomatous polyp of colon and cardiovascular disease share common risk factors. This cross-sectional study aims to investigate whether coronary calcification is associated with the adenomatous polyp of colon.

Methods: Among 2045 Korean adults, we examined the association between coronary calcium score(CCS) as a measurement of coronary calcification by Multi-detected row computed tomography (MDCT) and the presence of adenomatous polyp of colon as determined by colonoscopy. CCS values were categorized separately as follows: 0, 1-17, 18–105 and ≥106. The odds ratios (ORs) and 95% confidence intervals (CIs) for adenomatous polyp of colon were calculated across each group of CCS.

Results: After adjusting for confounding variables, the adjusted ORs (95% CIs) for adenomatous polyp of colon according to each of the four groups of CCS were 1.00(reference), 1.46 (0.92 – 2.32), 1.89 (1.17 – 2.99) and 3.57 (2.24 – 5.69).

Conclusion: A higher level of CCS was found to be independently and strongly associated with the presence of adenomatous polyp of colon, regardless of traditional cardiovascular risk factors among Korean adults. This finding suggests that people who have high risk for coronary atherosclerosis should be considered for further evaluation of adenomatous polyps of colon.

Key words : coronary calcium score, adenomatous polyp of colon, and cross-sectional study

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I. INTRODUCTION

Colon cancer is one of the most common malignancies and one of the leading causes of cancer death around the world.[1] Adenomatous polyp of colon is a precancerous lesion, and screening for detection and removal of them has been shown to reduce colorectal cancer mortality.[2]

In addition to the importance as precancerous lesion, there are many studies which have shown that the adenomatous polyp of colon is associated with the increased incidence and mortality of cardiovascular disease(CVD).[3,4] More

recent studies have also reported that the adenomatous polyp of colon is related to obesity[5,6], type 2 diabetes, and insulin resistance.[7,8] One study[9] demonstrated that a higher level of Pulse wave velocity (PWV), one of the reliable indicators of atherosclerosis, may be independently related with the presence of the adenomatous polyp of colon, regardless of conventional cardiovascular risk factors.

Coronary calcification is closely related with mural atheromatous plaque[10] that can be quantified by multi-detected row computed tomography(MDCT). The coronary calcium score(CCS) is proportionally associated with the severity of atherosclerotic disease.[11] In addition, CCS is a strong predictor of future coronary artery event, independent of the traditional risk factors.[12]

According to these findings, it can be analogized that there is a positive correlation between CCS and the adenomatous polyp of colon, although little has been written about the relationship between coronary calcification and adenomatous polyp of colon. Therefore, a cross-sectional study was performed to examine whether coronary calcification as determined by CCS is associated with adenomatous polyp of colon among Korean adults.

II. MATERIALS AND METHODS

1. Study population

The data of 2135 visitors between the ages of 18 and 83 who had been undertaken both MDCT and colonoscopy between January 2007 and October 2010 were collected from the health promotion center of Gangnam Severance Hospital in Seoul, Korea. Subjects meeting any of the following criteria were excluded: subjects with any missing covariate information; subjects with a history of colon disease such as ulcerative colitis or Crohn's disease, colorectal cancer, prior colonic surgery or prior colorectal polypectomy. After the exclusion criteria were applied, 2045 subjects (1224 men, 821 women between the ages of 18 and 82) were included in the study.

2. Data collection

We asked participants about their health behaviors including cigarette smoking and medical history including colonic disease. Completed questionnaires were reviewed by trained staff members and entered into a database. Physical examinations were performed by trained medical staff following a standardized

procedure.

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively in light indoor clothing. We defined the diagnosis of obesity as a BMI of ≥ 25 kg/m^2, suggested by the position statement of the American College of Endocrinology.[13,14] Blood pressure was measured in the right arm using a standard mercury sphygmomanometer (Baumanometer). Venous blood was collected after a 12-h fast from the antecubital vein.

Fasting plasma glucose(FPG), total cholesterol, high-density lipoprotein(HDL) cholesterol, low-density lipoprotein(LDL) cholesterol, triglyceride, alanine aminotransferase(ALT) and high-sensitive C-reactive protein(CRP) were measured using the Hitachi 7600-110 automated chemistry analyzer (Hitachi, Tokyo, Japan).

3. Multi-detected row computed tomography (MDCT)

Computed tomography coronary angiography (CTCA) was performed using a 64-MDCT scanner (Philips Brilliance 64, Philips Medical System, Best, Netherlands). In the supine position, CTCA was performed in the craniocaudal direction within a single breath-hold at the end-inspiratory suspension. 1.0

mL/kg of iodinated contrast medium (Optiray 350; Tyco healthcare, Kantata, Canada) was administered intravenously at a rate of 5 mL/s, followed by 50 mL of normal saline at a rate of 5 mL/s using a power injector (Nemoto; Nemoto Kyorindo, Tokyo, Japan). Imaging was performed using real time bolus tracking where a region of interest was located at the ascending aorta. The scans were started 7 s after reaching a trigger threshold of 110 Hounsfield Units (HUs). The scanning parameters were as follows: step-and-shoot axial scanning direction, 420-ms gantry rotation time, 120 kV, 210 mAs, 64=0.625-mm slice collimation, and 4-cm table feed per rotation. Image reconstruction was performed on the scanner's workstation using commercially available software (Extended Brilliance Workstation, Philips Medical System, Best, Netherlands).

A stack of cardiac images are obtained in an axial mode and calcified plaque is identified. This calcified plaque image is seen as white dots which are picture elements or pixels with an underlying number called HUs. Based on the HU numbers assigned to a pixel and its volume, we arrive at a CCS. Just like a value for hypertension, a HU value above 129 is considered dense enough to call it calcified and a weight factor is assigned, based on this number, to quantify the density. Total CCS is the sum of the scores of all the calcified lesions in all the vessels.[15]

4. Colonoscopy

We performed colonoscopy that at least reached the cecum after bowel preparation with bowel preparation with a lavage solution (45 ml, containing phosphotate 3mM/mL and 4mEq sodium/mL, Korea pharma.Co.).

Adenomatous polyps of colon were defined when discrete mass lesions protruding into the intestinal lumen were found during colonoscopy and a professional pathologist confirmed the lesions as adenomatous polyp at biopsy.

We conducted the colonoscopic procedures, including the size, number, histologic findings, and advanced lesion of the adenomatous polyp of colon. The size of a polyp was assessed by comparing it with an open colonoscopy biopsy forceps (Bard, Murray Hill, N.J., USA), and was classified either <10 or ≥10 mm (the largest size used for multiple polyps). The number of polyps was classified into either ≤2 or multiple (≥3) adenomas. Also, advanced adenomatous polyp of colon was defined as follows; ≥1 cm in estimated diameter or ≥3 polyps or containing ≥25% villous features and/or high-grade dysplasia.

5. Statistical Analysis

CCS values were categorized separately as follows: 0, 1−17, 18-105, and ≥106. Because of the numerous subjects whose CCS equals 0, subjects whose CCS is higher than 0 are categorized into tertiles. Then, four subject groups including the subject group whose CCS equals 0 are compared with each other.

The basic characteristics of the study population according to the four groups of CCS were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for adenomatous polyp of colon were calculated after adjusting for confounding variables between two groups of CCS using multivariate logistic regression analyses. All analyses were conducted using SPSS statistical software, version 12.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a p-value of <0.05 was considered significant.

III. RESULTS

The data of a total of 2045 subjects (1224 males and 821 females; age: 18-82 years) were collected for final analysis. The prevalence of the overall adenomatous polyp of colon was 474(23.2%). Table 1 shows the demographic and biochemical characteristics of subjects according to CCS. The average age of all subjects was 52 years (51.9± 9.3, data not shown). The mean BMI (kg/m2) was 23.4 and the total percentage of current smokers was 32.7%. The mean age, number of male subjects, BMI, SBP, DBP, FPG, and ALT level were higher in the CCS ≥ 106 group, whereas percentage of current smokers was lower in that group. Triglyceride level was highest in CCS 18-105 group among four groups.

Based on multiple logistic regression analysis of whole 2045 subjects, old age, male sex, triglyceride, current smoking and CCS were significant risk factor for adenomatous polyp of colon. (Table 2)

The prevalence of adenomatous polyp of colon increased as CCS values went up: 17.5%(278/1588), 31.8%(49/154), 38.0%(57/150) and 58.8%(90/153) corresponded with the groups with CCS=0, 1–17, 18–105, ≥106, respectively ($p < 0.001$) (Fig. 1).

Table 3 shows the risk of the adenomatous polyp of colon according to the

CCS values. After adjusting for age, smoking status, body mass index, blood pressure, fasting glucose, total cholesterol, triglyceride, HDL- cholesterol and LDL-cholesterol, the adjusted OR (95% CI) of adenomatous polyp of colon for the highest group of CCS was 4.47 (2.87 – 6.99) compared to the lowest group. We also assessed the association between CCS values and risk of adenomatous polyp of colon after additional adjusting for sex, ALT and C-reactive protein (Model 3), and the prevalence risk of adenomatous polyp of colon for the highest group of CCS was 3.57 (95% CI 2.24 – 5.69).

As shown in Table 4, compared to the subject group whose CCS equals 0, the higher the CCS values, multiple colon polyps($p<0.001$), villous histologic feature or high-grade dysplasia($p=0.02$) and advanced adenomatous polyp of colon($p<0.001$) occurs more frequently. However, there is no correlation between the CCS value and the size of colon polyps.

Table 1. Characteristics according to coronary calcium score value[a]

	CCS value				P-value[b]
	0(n=1588)	1-17(n=154)	18-105(n=150)	≥106(n=153)	
Age(years)	50.2±8.5	55.3±9.0	57.4±9.0	61.5±8.8	<0.001
Male sex(%)	51.8	77.5	87.3	86.0	<0.001
Current smokers(%)	35.6	29.4	23.3	21.5	<0.001
Body mass index(kg/m^2)	23.1±2.8	24.5±2.8	24.0±2.4	24.5±2.4	<0.001
Systolic BP(mmHg)	119.5±15.9	123.7±16.8	125.0±14.8	128.6±13.1	<0.001
Diastolic BP(mmHg)	74.5±9.6	77.9±8.3	78.8±9.1	80.5±7.8	<0.001
hsCRP(mg/L)	1.4±2.4	1.7±2.1	1.6±2.3	1.9±2.8	0.16
Fasting glucose(mg/dL)	92.0±13.7	95.6±12.6	99.2±21.4	105.8±29.8	<0.001
Total cholesterol(mg/dL)	201.4±78.2	197.5±69.8	210.4±80.2	205.9±67.3	0.46
Triglyceride(mg/dL)	113.1±70.3	124.7±68.5	134.8±83.1	125.9±56.4	0.002
HDL cholesterol(mg/dL)	47.8±11.4	41.8±9.9	54.3±12.0	48.8±17.2	0.42
LDL cholesterol(mg/dL)	122.4± 30.0	125.8±30.5	124.7±31.2	121.0±31.4	0.53
ALT(IU/L)	23.9±15.2	29.1±18.3	24.6±10.0	27.7±14.7	<0.001

Abbreviations: BP = blood pressure; hsCRP = high-sensitive C-reactive protein; HDL = high density lipoprotein; LDL = low density lipoprotein; ALT = alanine aminotransferase.

[a]Data are expressed as the mean ± standard deviation or percentage.

[b]P-value was calculated by ANOVA test for continuous variable or chi-squared test for categorical variable.

Table 2. Odds ratio drawn from multiple logistic regression analysis between contributing parameters and adenomatous polyp of colon

	Odds ratio (95% confidence interval)		p-value
Age (years)	4.62	(2.87 – 7.45)	<0.001
Male sex	2.48	(1.73 – 3.55)	<0.001
Current smoker (vs. never)	1.95	(1.39 – 2.76)	<0.001
BMI (kg/m2)	1.18	(0.73 – 1.88)	0.50
SBP (mmHg)	1.60	(0.83 – 3.08)	0.16
DBP (mmHg)	0.73	(0.38 – 1.40)	0.35
Fasting glucose (mg/dL)	0.87	(0.57 – 1.34)	0.54
Total cholesterol(mg/dL)	1.24	(0.78 – 1.95)	0.51
LDL-C (mg/dL)	1.01	(0.68 – 1.50)	0.97
HDL-C (mg/dL)	0.81	(0.45 – 1.38)	0.46
Triglyceride (mg/dL)	1.92	(1.22 – 3.02)	0.005
ALT (IU/L)	0.72	(0.47 – 1.11)	0.14
hsCRP (mg/L)	1.02	(0.68 – 1.53)	0.92
CCS	3.59	(2.26 – 5.71)	<0.001

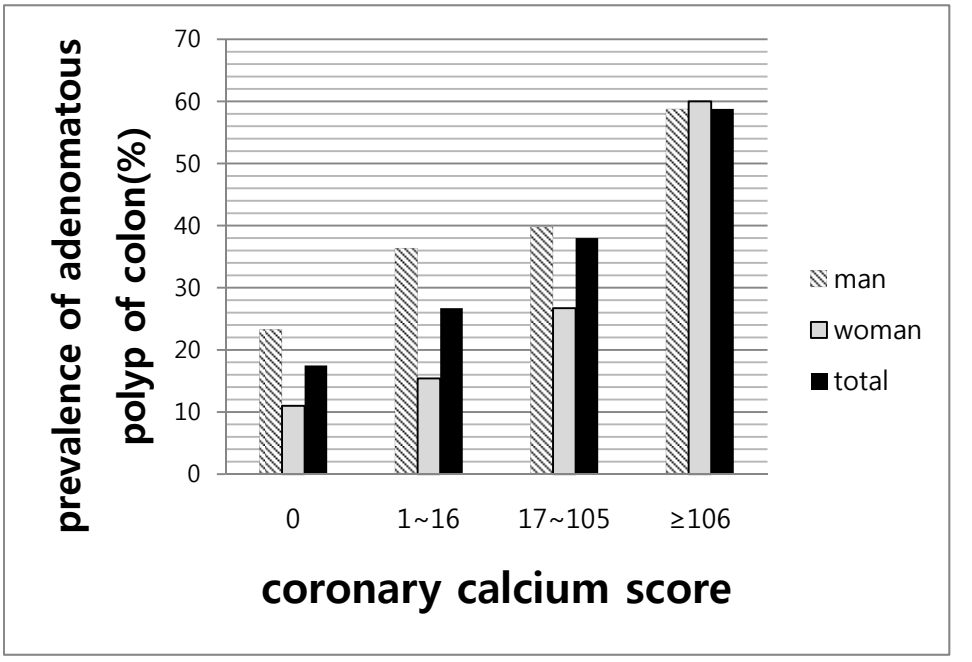

Figure1. Comparison of the prevalent adenomatous polyp of colon according to the coronary calcium score

Table 3. Odds ratio and 95% confidence intervals for adenomatous polyp of colon according to CCS value.

	CCS value			
	0	1-17	18-105	≥106
Model 1[a]	1.00	2.18 (1.43 – 3.32)	2.90 (1.93 – 4.36)	6.79 (4.56 – 10.10)
Model 2[b]	1.00	1.60 (1.01 – 2.53)	2.30 (1.48 – 3.58)	4.47 (2.87 – 6.99)
Model 3[c]	1.00	1.46 (0.92 – 2.32)	1.89 (1.17 – 2.99)	3.57 (2.24 – 5.69)

[a]Model 1: unadjusted.

[b]Model 2: adjusted for age, smoking status, body mass index, blood pressure, fasting glucose, total cholesterol, triglyceride, HDL- cholesterol and LDL-cholesterol

[c]Model 3: adjusted for age, sex, smoking status, body mass index, blood pressure, high sensitive C-reactive protein, fasting glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol and alanine aminotransferase

Table 4. Characteristics of adenomatous polyp of colon categorized by CCS

	CCS value				p-value
	0 (n=1588)	1-17 (n=154)	18-105 (n=150)	≥106(n=153)	
Colon polyp (%)	278(17.5)	49(31.8)	57(38.0)	90(58.8)	<0.001
Size(mm)					
<10	251 (90.3%)	46 (93.9%)	54 (94.7%)	81 (90.0%)	0.63
≥10	27 (9.7%)	3 (6.1%)	3 (5.3%)	9 (10.0%)	
Number					
<3	246 (88.5%)	38 (77.6%)	42 (73.7%)	52 (57.8%)	<0.001
≥3	32 (11.5%)	11 (22.4%)	15 (26.3%)	38 (42.2%)	
Villous feature or high-grade dysplasia					
Yes	0 (0%)	0 (0%)	1 (1.8%)	4 (4.4%)	0.02
No	278 (100%)	49 (100%)	56 (98.2%)	86 (95.6%)	
Advanced lesion					
Yes	39 (17.6%)	11 (22.4%)	16 (28.1%)	41 (45.6%)	<0.001
No	239 (82.4%)	38 (77.6%)	41 (71.9%)	49 (54.4%)	

IV. DISCUSSION

In this population-based, cross-sectional study, we found that adenomatous polyp of colon can be positively related to high risk of coronary atherosclerosis in Korean adults. This association remained significant after adjusting for potentially confounding variables of coronary calcification.

MDCT is noninvasive, can be performed easily, and allows direct visualization of the coronary arteries. [16] The CCS detected by MDCT correlate moderately well with angiographic findings.[15, 18] Furthermore, CCS is a reasonable risk stratification tool in asymptomatic intermediate-risk patients.[19] Additionally, CCS can be used to assess progression or regression of coronary artery disease.[15]

There is a controversy about cur-off prognostic value of CCS for coronary artery disease.[17,19-22] Arad et al.[20] have shown that subjects with a calcium score >100 have more than a nine times greater risk for death due to coronary events compared to subjects with a calcium score ≤100 . The prospective Multi-Ethnic Study of Atherosclerosis(MESA)[17] reported that CCS between 101 and 300 was associated with a 7.7 increased risk of coronary events, whereas CCS >300 increased the risk of a factor of 9.67. Generally, the absence of CCS identifies

the subjects at a very low risk of cardiovascular events (<1% per year).[19] Therefore, we designated CCS value 0 as a reference group.

This study found that patients with high CCS have a higher risk of developing adenomatous polyp of colon and, therefore, it may lead to developing colorectal cancer. Thus, high atherosclerotic risk may increase the possibility of developing colorectal cancer.

Certain mechanisms could explain the significant relationship between CCS and adenomatous polyp of colon. Insulin resistance may be responsible for the growth of adenomatous polyp of colon.[23] Insulin may exert a proliferative effect on colonic tumor cells directly[24] or indirectly via the insulin-like growth factor pathway.[25]Another possible mechanism of this association could be explained by chronic low-grade inflammation. Recent studies suggested that inflammation plays a key role in the carcinogenic pathway of colorectal cancer, possibly promoting the progression of adenomatous polyp of colon to adenocarcinoma.[26-28] Regular nonsteroidal anti-inflammatory drug(NSAID) use is known to be inversely associated with the recurrence of advanced and non-advanced adenomatous polyp of colon.[29,30] Inflammation also plays a critical role in the pathology of atherosclerosis. Markers of inflammation, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-a (TNF-a), are

independently related to the severity of the atherosclerotic process.[31,32] Inflammatory cytokines also have an pivotal role in the initiation and progression of arterial calcification.[32,33] Moreover, common molecular mechanisms in atherosclerosis and colorectal carcinogenesis are now being uncovered. For example, the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) has been discovered to play a role during atherogenesis[34] and the early stages of colorectal carcinogenesis[35].

This study has several limitations. First, because the study subjects were volunteers visiting for health promotion, screening in a single hospital and appeared to be healthier than average individuals, the study population may not have been representative of the general population in Korea. Second, this study is a cross-sectional study; therefore, it is not possible to establish a causal relationship between CCS and adenomatous polyp of colon. Finally, we did not take into consideration the effect of other potential confounding variables, such as physical activity, alcohol consumption, family history of adenomatous polyp of colon, and a history of medications (aspirin or NSAIDs). Although, these confounding variables could be important factors of adenomatous polyp of colon and coronary calcification, they were not fully adjusted for in the statistical model, causing a possible residual confounding effect.

V. CONCLUSION

In summary, coronary calcification was strongly and independently associated with the presence and high risk of adenomatous polyp of colon in Korean adult. This finding suggests that people who have high risk for coronary atherosclerosis should be considered for further evaluation of adenomatous polyp of colon. Further research is warranted to better understand the pathophysiologic role of coronary atherosclerosis in the development of adenomatous polyp of colon.

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ABSTRACT (IN KOREAN)

한국 성인에서 관상 동맥 석회화 수치와 대장의 선종성 용종과의 연관성

<지도교수 이 혜리>

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배경 : 대장암은 가장 흔한 악성 종양 중 하나이며, 대장의 선종성 용종은 전암성 병변이어서 이에 대한 선별검사가 대장암에 의한 사망률을 낮출 수 있다. 최근 대장의 선종성 용종과 심혈관 질환 사이에 공통된 위험 요인이 있다는 연구들이 보고되고 있다. 이번 연구에서는 심혈관계 질환의 위험 인자 중 하나인 관상 동맥 석회화 수치와 대장의 선종성 용종과의 관련성에 관하여 살펴 보고자 한다.

방법: 강남 세브란스 병원 건강증진 센터를 방문한 2045명 (남자: 1224명, 여자: 821명)을 대상으로 한 관찰 연구이다. Multi-detected row computed tomography(MDCT)을 통해서 구한 관상 동맥 석회화 수치를 범주화하여 0,1-7 군, 18-105군, 106 이상인 군, 총 4군으로

인구 집단을 나누었다.

결과: 심혈관계 위험인자를 보정한 후 관상 동맥 석회화 수치를 범주화한 4군의 대장의 선종성 용종에 대한 위험도를 로짓 분석한 결과 1.00, 1.46 (0.92 - 2.32), 1.89 (1.17 - 2.99), 3.57 (2.24 - 5.69)이었다.

결론: 관상 동맥 석회화 수치가 높을수록 대장의 선종성 용종 발생의 위험도가 높다. 이러한 사실은 심혈관 질환의 위험성이 높은 사람은 대장의 선종성 용종의 발견을 위해 대장내시경 검사를 더욱 적극적으로 할 필요가 있다는 것을 시사한다.

핵심되는 말: 관상 동맥 석회화 수치, 대장의 선종성 용종, 단면 연구