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ORIGINAL ARTICLE

Dietary Calcium Intake and Colorectal Adenoma in Men and Women with Low Calcium Intake

Jioh Kang[1], Sang Hoon Kim[2], Joowon Chung[3], Dong Hyun Kim[4], Min Kyu Jung[5], Seun Ja Park[6], Hoon Jai Chun[7], Yun Jeong Lim[8], Hyun Jeong Cho[1], Jung Eun Lee[1,9]

[1]Department of Food and Nutrition, College of Human Ecology, Seoul National University, Seoul, [2]Division of Gastroenterology, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, [3]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, [4]Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, [6]Department of Internal Medicine, Kosin University College of Medicine, Busan, [7]Department of Internal Medicine, Institute of Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, [8]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Goyang, [9]Research Institute of Human Ecology, Seoul National University, Seoul, Korea

Backgrounds/Aims: Calcium is a preventive factor for colorectal cancer, which develops from colorectal adenoma. This study aimed to investigate the association between dietary calcium intake and prevalence of colorectal adenoma among Korean adults.
Methods: Overall, 612 participants aged ≥ 20 years who underwent gastrointestinal endoscopy at 8 medical centers from 2021 to 2023 were included. Dietary calcium intake was assessed using a food frequency questionnaire and was energy-adjusted using the residual model. Multivariate logistic regression models were used to calculate for the odds ratios (ORs) and 95% confidence intervals (CIs). The associations between dietary calcium intake and colorectal adenoma prevalence were also assessed according to the anatomic subsites and adenoma status (advanced or nonadvanced).
Results: Among the 612 participants, 269 were diagnosed with colorectal adenoma (170 men and 99 women). With respect to the gender-specific association, low dietary calcium intake was associated with higher prevalence of colorectal adenoma among men (ORs [95% CIs]: 2.13 [0.50–9.00] for < 250 mg/day; 3.53 [1.06–11.76], 250 to < 350 mg/day; and 1.84 [0.63–5.35], 350 to < 650 mg/day, compared to ≥ 650 mg/day of dietary calcium [p for trend = 0.07]). Similar association was observed among women, but neither the association nor trend was statistically significant (p for trend = 0.59). These inverse associations remained similar for distal colon/rectal adenoma among women and advanced adenoma among men.
Conclusions: Low dietary calcium intake was associated with high colorectal adenoma prevalence, particularly among men. Given the limited number of studies among Asian populations, our findings should be replicated in other Asian groups.

Key Words: Colorectal neoplasms; Calcium, dietary; Korea

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Corresponding author:
Hyun Jeong Cho
E-mail: 92hyunjung@snu.ac.kr
https://orcid.org/0000-0003-0055-2334
Corresponding author:
Jung Eun Lee
E-mail: jungelee@snu.ac.kr
https://orcid.org/0000-0003-1141-878X

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of death worldwide [1]. In Korea, colorectal cancer was the fourth most common cancer in men and the third most common cancer in women in 2020 [2]. Most colorectal cancer cases are thought to originate from colorectal adenomas through the accumulation of mutations leading to malignancy over time, and thus early detection and removal of adenomas are considered crucial steps in reducing colorectal cancer risk [3,4].

Calcium has been hypothesized to inhibit the development of colorectal neoplasia through several pathways, including suppressing cell growth and inducing apoptosis [5,6]. The World Cancer Research Fund (WCRF) has reported strong evidence that the consumption of dairy products and calcium supplements reduces the risk of colorectal cancer [7]. Epidemiological evidence suggests a preventive effect of calcium intake on the risk of colorectal adenomas. A meta-analysis of prospective studies found an inverse association between total calcium intake and the risk of colorectal adenomas [8].

Most prospective studies have been conducted in Western countries, including the US [9-14] and France [15], both of which reported higher dietary calcium intake compared to Asia. The mean dietary calcium intake in Asia, including Japan, China, and Korea, was reported to be less than 550 c, whereas it exceeded 800 mg/day in the US and several European countries, including France, Germany, and the UK [16]. Despite these regional disparities in calcium intake, few studies have assessed the association between calcium intake and colorectal adenoma in Asian populations [17-19]. Therefore, investigating the association between low dietary calcium intake and the prevalence of colorectal adenoma in populations with low calcium intake is both challenging and valuable for understanding potential preventive strategies.

Given the limited evidence on the association between calcium intake and colorectal cancer precursors in Asian populations, this cross-sectional study aimed to evaluate whether lower dietary calcium intake in Korean adults is associated with a higher prevalence of colorectal adenoma.

MATERIALS AND METHODS

Study population

This cross-sectional study included 1,198 participants who underwent gastrointestinal endoscopy at eight hospitals in Korea from July 2017 to October 2023. We excluded those with missing data on colorectal adenoma diagnosis (n = 366) or those diagnosed with colorectal cancer (n = 23), inflammatory bowel disease (n = 172), proctitis (n = 1), or hamartomatous polyps (n = 1). Participants with missing food frequency questionnaire (FFQ) data (n = 13), or implausible energy intake (more than 3 standard deviations above or below the mean of the log-transformed energy intake) (n = 10) were excluded, resulting in 612 participants included in the analysis. This study was approved by the Institutional Review Board at each hospital. Written informed consent was obtained from all participants: Chonnam National University (CNUH-2021-250), Chungnam National University Sejong Hospital (CNUSH 2021-08-002), Donguk University Hospital (DUIH 2021-03-030-005), Kyungpook National University Hospital (KNUH 2021-05-011), Chungbuk National University Hospital (CBNUH 2021-07-027-001), Kangwon National University Hospital (KNUH-A-2021-05-011-012), Eulji University Hospital (EMCS 2022-12-015), and Jeju National University Hospital (2021-06-005).

Assessment of calcium intake

Dietary calcium intake was assessed using a validated 113-item FFQ developed for the Korean population, with its validation and reliability previously documented [20]. Daily calcium intake was calculated for each food item by multiplying the reported frequency of consumption by the quantity consumed and then multiplying this amount by the calcium content per portion, as detailed in the eighth edition of the Korean Food Composition Table (KFCT) [21]. These values were then summed to obtain the average daily dietary calcium intake for each participant. Participants provided detailed information about their use of calcium supplements, including the type, name, duration, and daily intake, through a structured questionnaire. The calcium content per serving for each supplement was obtained from the manufacturers' nutrition facts labels. Supplemental calcium intake was calculated by multiplying the daily intake by the calcium content per serving in the supplement.

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Assessment of covariates

Sociodemographic, lifestyle, and clinical characteristics of participants were collected at the time of colonoscopy using a structured questionnaire. This included information on age, gender, smoking status, physical activity, education level, menopausal status, history of colon polyp resection, family history of colorectal cancer, hypertension, diabetes, and aspirin use. Details about smoking were collected, including current smoking status, the number of packs smoked currently or in the past, the age at smoking initiation, and the age at quitting. Pack-years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Physical activity was assessed by calculating the metabolic equivalent of tasks (METs) hours per week, based on the average minutes and days spent on various activities [22]. Height and weight were measured at each hospital, and body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). Diabetes and hypertension were defined by self-reported current status or the use of hypoglycemic or antihypertensive medications. Alcohol, dietary fiber, and red and processed meat intakes were assessed through the FFQ. Alcohol intake was measured in grams per day (g/d) and calculated from the total ethanol content of beer, soju, wine, and rice wine consumed over the past year.

Ascertainment of colorectal adenomas

Colorectal adenomas were confirmed through colonoscopy and histopathological examination by trained gastroenterologists at each hospital. The anatomical subsites of colorectal adenomas were classified into three sections: proximal colon, distal colon, and rectum. The proximal colon includes the cecum, ascending colon, and transverse colon, while the distal colon comprises the descending and sigmoid colon. Cases with one or more proximal colon adenomas, but no distal colon or rectal adenomas, were classified into the proximal colon adenoma group. Similarly, cases with one or more distal colon or rectal adenomas, but no proximal colon adenomas, were classified into the distal colon/rectal adenoma group. Additionally, a multiple location adenoma group was established, including cases with adenomas in various anatomical sites within the colorectum (i.e., proximal colon, distal colon, and rectum). Advanced adenomas were defined as those with villous components, a diameter of ≥ 10 mm, or high-grade dysplasia.

Statistical analysis

Dietary calcium intake was adjusted for energy intake using the residual model [23]. For the gender-specific analyses, dietary calcium intake was categorized into 4 groups: < 250, 250 to < 350, 350 to < 650, and ≥ 650 mg/day for men, and < 350, 350 to < 650, 650 to < 750, and ≥ 750 mg/day for women. For the analysis of all participants, dietary calcium intake was categorized into 5 groups: < 250, 250 to < 350, 350 to < 650, 650 to < 750, and ≥ 750 mg/day. We categorized dietary calcium intake to ensure a decent number of cases for analysis, reflecting gender-specific distributions. Total calcium intake was calculated by summing the energy-adjusted dietary intake and the supplemental intake. The cutoffs for total calcium intake were determined similarly to those for dietary calcium intake. Supplemental calcium intake was categorized into 3 groups, non-user, below median (men: 210 mg/day, women: 280 mg/day, and all participants: 240 mg/day), and at or above the median.

To assess the association of the calcium intake with the prevalence of colorectal adenoma, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models. In the multivariate model, we adjusted for age (years, continuous), gender (men or women), BMI (< 23, 23 to < 25, or ≥ 25 kg/m^2), smoking status (men: never, past smoker with pack-years missing, < 19.9 pack-years, ≥ 19.9 pack-years, current smokers with < 18.8 pack-years, or ≥ 18.8 pack-years; women: never or ever), alcohol intake (men: none, < 40, 40 to < 90, 90 to < 170, 170 to < 320, or ≥ 320 g/d; women: none, < 20, 20 to < 100, or ≥ 100 g/d), physical activities (none, 0 to < 15, or ≥ 15 METs-hour/week), education level (middle school or below, high school, or college or above), history of colon polyp resection (never, < 2, 2 to < 4, or ≥ 4 years), hypertension (yes or no), diabetes (yes or no), aspirin use (yes or no), dietary fiber intake (< 15, 15 to < 20, 20 to < 25, 25 to < 35, or ≥ 35 g/d), and red/processed meat intake (g/d, continuous). The proportion of missing pack-years was 7% for past smokers. We included postmenopausal status (premenopausal or postmenopausal) in the women-specific analysis. To examine trends across the groups, median values of each group were used as continuous variables in the model.

We assessed the potential non-linear association between dietary calcium intake and colorectal adenoma using a restricted cubic spline curve with 4 knots for dietary calcium intake, and calculated the p value for curvature. The reference values were the median value of the highest group of dietary calcium (773.9 mg/day for men; 955.6 mg/day for women; 893.0 mg/day for all particiapants). Participants in the top 1% of dietary calcium intake were excluded from the analysis when using the spline curve.

We also explored the association between dietary calcium intake and the prevalence of colorectal adenoma according to polyp features, including anatomic subsite and adenoma status. When analyzing by anatomic subsite, participants with adenomas in the proximal colon, distal colon/rectum, or multiple locations were compared to those without any adenomas. For the analysis by adenoma status, participants with missing information on adenoma status (n = 37) were excluded, and those with non-advanced or advanced adenomas were compared to those without adenomas.

We examined whether the associations differed by potential effect modifiers, including age (< 57 or ≥ 57 years), BMI (< 25 or ≥ 25 kg/m^2), smoking status (never or ever), and alcohol drinking (non-drinkers or drinkers). A likelihood ratio test was used in the logistic regression model to estimate the p value for interaction by adding a cross-product interaction term between dietary calcium intake and these variables. All statistical analyses were performed using SAS version 9.4 (SAS Institute), and two-sided p values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of participants

Out of 612 participants, 269 were diagnosed with colorectal adenoma, including 170 men and 99 women. Among these 269 cases, 119 were diagnosed with proximal colon adenoma, 79 with distal colon/rectal adenoma (63 for distal colon only, 12 for rectal adenoma only, and 4 for both) and 71 with adenomas in multiple locations. Additionally, 102 cases were identified as advanced adenoma. The median intake of dietary calcium was 447.5 mg/day among all participants, with 421.5 mg/day among men and 489.0 mg/day among women (Supplementary Table 1, Table 1). Participants in the lowest dietary calcium intake group were younger, less physically active, drank more alcohol, and smoked more compared to those in the highest intake group (Supplementary Table 1). They also had lower dietary fiber intake and red/processed meat intake, less frequent use of dietary supplements, a lower proportion who had never undergone polyp resection, a lower proportion with a family history of colorectal cancer, and a lower prevalence of hypertension and diabetes. The characteristics observed in men and women according to dietary calcium were similar to those of the total population, with some differences noted (Table 1). Men with the lowest calcium intake smoked less and used aspirin less frequently compared to those with the highest intake. Among women, those in the lowest intake group consumed more red and processed meat, had a lower proportion of postmenopausal women, and used aspirin more frequently.

Association between calcium intake and colorectal adenoma

There was a suggestive association between low dietary calcium intake and a high prevalence of colorectal adenoma (Table 2). Among men, lower dietary calcium intake was associated with a higher prevalence of colorectal adenoma; the ORs (95% CIs) were 2.13 (0.50–9.00) for < 250 mg/day, 3.53 (1.06–11.76) for 250 to < 350 mg/day, and 1.84 (0.63–5.35)

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Table 1. Characteristics of Study Participants according to Dietary Calcium Intake in Men and Women

Variable*	Men (n = 325)					Women (n = 287)				
	All	Categories of dietary calcium intake (mg/day)				All	Categories of dietary calcium intake (mg/day)			
		< 250	250 to < 350	350 to < 650	≥ 650		< 350	350 to < 650	650 to < 750	≥ 750
Dietary calcium intake (mg/day), median†	421.5	209.8	313.9	452.0	773.9	489.0	308.1	467.2	680.2	955.6
Age (yr)	55.4 ± 12.5	54.0 ± 12.6	54.7 ± 12.6	55.1 ± 12.7	61.2 ± 10.1	55.2 ± 12.9	52.8 ± 16.8	54.4 ± 12.3	58.1 ± 9.7	60.0 ± 10.8
BMI (kg/m^2)	25.0 ± 3.1	24.6 ± 3.1	25.1 ± 3.1	25.0 ± 3.2	24.8 ± 2.4	22.8 ± 3.3	22.2 ± 3.4	22.8 ± 3.2	22.9 ± 3.3	23.2 ± 3.5
Physical activity (METs-hr/wk)	25.6 ± 31.4	25.2 ± 31.5	29.4 ± 39.0	24.5 ± 29.8	25.8 ± 21.9	22.0 ± 38.0	20.0 ± 27.0	19.9 ± 28.3	24.6 ± 22.2	32.3 ± 76.3
Alcohol intake (g/day)	163.9 ± 320.1	238.0 ± 521.2	237.5 ± 371.2	147.1 ± 284.9	44.0 ± 51.5	33.9 ± 91.5	63.4 ± 157.1	34.3 ± 80.2	11.0 ± 33.3	13.3 ± 46.2
Smoking (pack-years)	17.8 ± 20.5	16.2 ± 24.5	20.4 ± 20.5	16.4 ± 19.5	25.4 ± 23.6	0.8 ± 4.6	0.7 ± 4.0	1.0 ± 5.4	0.0 ± 0.0	0.4 ± 1.7
Education level‡										
Middle school or below	43 (13.3)	3 (12.0)	9 (13.8)	24 (11.5)	7 (26.9)	51 (17.9)	10 (22.7)	29 (16.5)	4 (15.4)	8 (20.5)
High school	120 (37.0)	14 (56.0)	25 (38.5)	73 (35.1)	8 (30.8)	114 (40.0)	13 (29.5)	66 (37.5)	14 (53.8)	21 (53.8)
College or above	161 (49.7)	8 (32.0)	31 (47.7)	111 (53.4)	11 (42.3)	120 (42.1)	21 (47.7)	81 (46.0)	8 (30.8)	10 (25.6)
Energy intake (kcal/day)	2,272 ± 1,101.0	1,991 ± 788.0	2,169 ± 938.4	2,375 ± 1,166.0	1,971 ± 1,123.0	1,825 ± 909.2	1,831 ± 733.4	1,799 ± 850.6	2,058 ± 895.0	1,780 ± 1,296.0
Dietary fiber intake (g/day)	18.6 ± 6.2	10.5 ± 3.1	15.7 ± 4.1	19.9 ± 5.7	23.5 ± 7.0	24.2 ± 8.7	17.6 ± 4.0	23.6 ± 7.5	29.5 ± 9.1	30.7 ± 10.9

Table 1. Continued

Variable[cc]	Men (n = 325)					Women (n = 287)				
	All	Categories of dietary calcium intake (mg/day)				All	Categories of dietary calcium intake (mg/day)			
		< 250	250 to < 350	350 to < 650	≥ 650		< 350	350 to < 650	650 to < 750	≥ 750
Red/processed meat intake (g/day)	104.1 ± 115.8	53.6 ± 42.9	80.3 ± 76.5	118.1 ± 130.3	99.4 ± 101.5	69.4 ± 77.6	67.5 ± 73.4	68.1 ± 71.5	93.4 ± 103.4	61.5 ± 88.7
Supplement use										
Non-users	167 (51.4)	14 (56.0)	33 (50.8)	111 (53.1)	9 (34.6)	128 (44.6)	23 (51.1)	80 (45.2)	8 (30.8)	17 (43.6)
Users	158 (48.6)	11 (44.0)	32 (49.2)	98 (46.9)	17 (65.4)	159 (55.4)	22 (48.9)	97 (54.8)	18 (69.2)	22 (56.4)
Menopausal status[‡]										
Premeno-pausal	N/A	N/A	N/A	N/A	N/A	98 (35.5)	19 (44.2)	64 (37.6)	8 (30.8)	7 (18.9)
Postmeno-pausal	N/A	N/A	N/A	N/A	N/A	178 (64.5)	24 (55.8)	106 (62.4)	18 (69.2)	30 (81.1)
History of polyp resection[‡]										
Never	140 (43.2)	9 (36.0)	24 (36.9)	94 (45.2)	13 (50.0)	151 (53.2)	22 (50.0)	93 (53.1)	13 (50.0)	23 (59.0)
< 2 yr	57 (17.6)	4 (16.0)	13 (20.0)	38 (18.3)	2 (7.7)	36 (12.7)	5 (11.4)	24 (13.7)	3 (11.5)	4 (10.3)
2 to < 4 yr	61 (18.8)	5 (20.0)	11 (16.9)	41 (19.7)	4 (15.4)	43 (15.1)	8 (18.2)	25 (14.3)	2 (7.7)	8 (20.5)
≥ 4 yr	66 (20.4)	7 (28.0)	17 (26.2)	35 (16.8)	7 (26.9)	54 (19.0)	9 (20.5)	33 (18.9)	8 (30.8)	4 (10.3)
Family history of colorectal cancer[‡]										
No	294 (90.7)	25 (100.0)	61 (93.8)	185 (88.9)	23 (88.5)	254 (88.5)	39 (86.7)	161 (91.0)	22 (84.6)	32 (82.1)
Yes	30 (9.3)	0 (0)	4 (6.2)	23 (11.1)	3 (11.5)	33 (11.5)	6 (13.3)	16 (9.0)	4 (15.4)	7 (17.9)

Table 1. Continued

Variable*	Men (n = 325)					Women (n = 287)				
	All	Categories of dietary calcium intake (mg/day)				All	Categories of dietary calcium intake (mg/day)			
		< 250	250 to < 350	350 to < 650	≥ 650		< 350	350 to < 650	650 to < 750	≥ 750
Aspirin use										
No	291 (89.5)	24 (96.0)	58 (89.2)	187 (89.5)	22 (84.6)	277 (96.5)	41 (91.1)	173 (97.7)	25 (96.2)	38 (97.4)
Yes	34 (10.5)	1 (4.0)	7 (10.8)	22 (10.5)	4 (15.4)	10 (3.5)	4 (8.9)	4 (2.3)	1 (3.8)	1 (2.6)
Diabetes										
No	256 (78.8)	24 (96.0)	51 (78.5)	160 (76.6)	21 (80.8)	252 (87.8)	37 (82.2)	157 (88.7)	26 (100.0)	32 (82.1)
Yes	69 (21.2)	1 (4.0)	14 (21.5)	49 (23.4)	5 (19.2)	35 (12.2)	8 (17.8)	20 (11.3)	0 (0)	7 (17.9)
Hypertension										
No	193 (59.4)	18 (72.0)	33 (50.8)	131 (62.7)	11 (42.3)	217 (75.6)	29 (64.4)	141 (79.7)	21 (80.8)	26 (66.7)
Yes	132 (40.6)	7 (28.0)	32 (49.2)	78 (37.3)	15 (57.7)	70 (24.4)	16 (35.6)	36 (20.3)	5 (19.2)	13 (33.3)

BMI, body mass index; MET, metabolic equivalents; N/A, not applicable; yr, years.

*Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as n (%).

†Energy-adjusted dietary calcium intake.

‡Total number of participants is not equal to 325 for men and 287 for women due to missing information for some participants.

Table 2. ORs and 95% CIs for the Associations between Dietary Calcium Intake and Colorectal Adenoma

	Categories of dietary calcium intake (mg/day)					p for trend
Men	< 250	250 to < 350	350 to < 650	≥ 650		
No. of cases/total	14/25	41/65	106/209	9/26		
OR (95% CIs)*	3.28 (1.02–10.51)	4.34 (1.62–11.61)	2.50 (1.04–6.00)	1 (reference)		0.005
OR (95% CIs)†	2.13 (0.50–9.00)	3.53 (1.06–11.76)	1.84 (0.63–5.35)	1 (reference)		0.07
Women	< 350	350 to < 650	650 to < 750	≥ 750		
No. of cases/total	14/45	62/177	11/26	12/39		
OR (95% CIs)*	1.47 (0.54–4.02)	1.80 (0.81–4.00)	2.03 (0.68–6.03)	1 (reference)		0.31
OR (95% CIs)†	1.21 (0.35–4.13)	1.66 (0.66–4.19)	2.58 (0.76–8.75)	1 (reference)		0.59
All participants	< 250	250 to < 350	350 to < 650	650 to < 750	≥ 750	
No. of cases/total	15/32	54/103	168/386	16/37	16/54	
OR (95% CIs)*	2.03 (0.77–5.32)	2.97 (1.40–6.29)	2.03 (1.06–3.90)	1.86 (0.75–4.64)	1 (reference)	0.01
OR (95% CIs)†	1.31 (0.44–3.86)	2.46 (1.06–5.75)	1.78 (0.87–3.65)	2.54 (0.97–6.65)	1 (reference)	0.20

OR, odds ratio; CIs, confidence intervals.
*Model was adjusted for age (years, continuous) and gender (men or women, applicable only for all participants).
†Model was additionally adjusted for alcohol consumption (men: none, < 40, 40 to < 90, 90 to < 170, 170 to < 320, or ≥ 320 g/day; women: none, < 20, 20 to < 100, or ≥ 100 g/day), smoking status (men: never, past smoker with pack-years missing, < 19.9 pack-years, ≥ 19.9 pack-years, current smokers with < 18.8 pack-years, or ≥ 18.8 pack-years; women: never or ever), education level (middle school or below, high school, or college or above), physical activity (none, 0 to < 15, or ≥ 15 metabolic equivalents-hour/week), body mass index (< 23, 23 to < 25, or ≥ 25 kg/m^2), history of polyp resection (never, < 2, 2 to < 4, or ≥ 4 years), family history of colorectal cancer (yes or no), aspirin use (yes or no), hypertension (yes or no), diabetes (yes or no), dietary fiber intake (< 15, 15 to < 20, 20 to < 25, 25 to < 35, or ≥ 35 g/day), red/processed meat intake (g/day, continuous), and menopausal status (premenopausal or postmenopausal, applicable only for women).

for 350 to < 650 mg/day, compared to ≥ 650 mg/day of dietary calcium intake (p for trend = 0.07). Among women, a similar association was observed, but it was not statistically significant; the ORs (95% CIs) were 1.21 (0.35–4.13) for < 350 mg/day, 1.66 (0.66–4.19) for 350 to < 650 mg/day, and 2.58 (0.76–8.75) for 650 to < 750 mg/day, compared to ≥ 750 mg/day of dietary calcium intake (p for trend = 0.59). When including all participants, the ORs (95% CIs) were 1.31 (0.44–3.86) for < 250 mg/day, 2.46 (1.06–5.75) for 250 to < 350 mg/day, 1.78 (0.87–3.65) for 350 to < 650 mg/day, and 2.54 (0.97–6.65) for 650 to < 750 mg/day, compared to ≥ 750 mg/day of dietary calcium intake (p for trend = 0.20). When analyzing the data by quartiles in both men and women, the associations were attenuated, potentially due to a higher median value in the lowest quartile (290.3 mg/day for men, 336.5 mg/day for women) and a lower median value in the highest quartile (609.7 mg/day for men, 769.5 mg/day for women) compared to the analysis based on absolute dietary calcium cutoffs (Median: 209.8 mg/day for men and 308.1 mg/day for women in the lowest; 773.9 mg/day for men and 955.6 mg/day for women in the highest group) (Supplementary Table 2).

When examining the association between total calcium intake and colorectal adenoma (Supplementary Table 3), similar results were observed among men (p for trend = 0.07). However, further analysis of supplemental calcium intake revealed no association with the prevalence of colorectal adenoma (Supplementary Table 4).

Using a restricted cubic spline curve to examine the potential nonlinear relationship between dietary calcium intake and the prevalence of colorectal adenoma, we found no evidence of nonlinearity (p for curvature = 0.93, 0.11, and 0.54 for men, women, and all participants, respectively) (Supplementary Fig. 1).

In the analysis by anatomic subsite, potential inverse associations were found between distal colon/rectal adenoma in women and adenomas in multiple location in men, but these were not statistically significant (Table 3). The OR (95% CIs) of distal colon/rectal adenoma in women was 1.40 (0.35–5.64) for < 400 mg/day compared to ≥ 600 mg/day of dietary calcium intake (p for trend = 0.63), and the OR (95% CIs) of adenomas in multiple location among men was 2.12 (0.36–12.68) for < 300 mg/day compared to ≥ 600 mg/day of

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Table 3. ORs and 95% CIs for Associations between Dietary Calcium Intake and Colorectal Adenoma by Polyp Features

Polyp feature	Men				Women				All participants				
	Dietary calcium intake (mg/day)			p for trend	Dietary calcium intake (mg/day)			p for trend	Dietary calcium intake (mg/day)				p for trend
	< 300	300 to < 600	≥ 600		< 400	400 to < 600	≥ 600		< 250	250 to < 350	350 to < 650	≥ 650	
Anatomical subsite*													
Proximal colon adenoma													
No. of cases/total	12/34	52/159	10/36		11/62	16/101	18/70		7/24	22/71	77/295	13/72	
OR (95% CIs)	1.07 (0.23–5.04)	0.79 (0.27–2.37)	1 (reference)	0.97	0.89 (0.23–3.34)	0.83 (0.31–2.23)	1 (reference)	0.78	1.01 (0.27–3.84)	1.98 (0.73–5.38)	1.59 (0.74–3.42)	1 (reference)	0.34
Distal colon/rectal adenoma													
No. of cases/total	6/28	38/145	7/33		8/59	12/97	8/60		6/23	14/63	48/266	11/70	
OR (95% CIs)	0.67 (0.13–3.61)	1.35 (0.40–4.52)	1 (reference)	0.77	1.40 (0.35–5.64)	1.27 (0.39–4.15)	1 (reference)	0.63	1.32 (0.33–5.29)	1.38 (0.47–4.07)	1.13 (0.49–2.64)	1 (reference)	0.59
Multiple adenomas													
No. of cases/total	8/30	32/139	5/31		9/60	9/94	8/60		2/19	18/67	43/261	8/67	
OR (95% CIs)	2.12 (0.36–12.68)	1.52 (0.38–6.11)	1 (reference)	0.41	0.49 (0.10–2.55)	0.38 (0.10–1.49)	1 (reference)	0.26	0.27 (0.04–1.76)	1.28 (0.39–4.20)	0.85 (0.32–2.27)	1 (reference)	0.66
Adenoma status†													
Non-advanced adenoma													
No. of cases/total	10/32	63/170	10/36		10/61	23/108	14/66		5/22	24/73	89/307	12/71	
OR (95% CIs)	0.58 (0.15–2.30)	1.03 (0.38–2.80)	1 (reference)	0.52	1.14 (0.34–3.83)	1.13 (0.45–2.87)	1 (reference)	0.80	0.87 (0.22–3.44)	2.11 (0.80–5.57)	1.85 (0.86–4.02)	1 (reference)	0.30

Table 3. Continued

Polyp feature	Men				Women				All participants				
	Dietary calcium intake (mg/day)			p for trend	Dietary calcium intake (mg/day)			p for trend	Dietary calcium intake (mg/day)				p for trend
	< 300	300 to < 600	≥ 600		< 400	400 to < 600	≥ 600		< 250	250 to < 350	350 to < 650	≥ 650	
Advanced adenoma													
No. of cases/total	15/37	41/148	8/34		10/61	12/97	16/68		9/26	23/72	55/273	15/74	
OR (95% CIs)	2.47 (0.54–11.37)	1.27 (0.38–4.22)	1 (reference)	0.25	0.53 (0.14–1.99)	0.54 (0.19–1.54)	1 (reference)	0.26	0.96 (0.27–3.38)	1.45 (0.55–3.81)	0.81 (0.38–1.73)	1 (reference)	0.79

OR, odds ratio; CIs, confidence intervals.

All models were adjusted for age (years, continuous), gender (men or women, applicable only for all participants), alcohol consumption (men: none, < 40, 40 to < 90, 90 to < 170, 170 to < 320, or ≥ 320 g/day; women: none, < 20, 20 to < 100, or ≥ 100 g/day), smoking status (men: never, past smoker with pack-years missing, < 19.9 pack-years, ≥ 19.9 pack-years, current smokers with < 18.8 pack-years, or ≥ 18.8 pack-years; women: never or ever), education level (middle school or below, high school, or college or above), physical activity (none, 0 to < 15, or ≥ 15 metabolic equivalents-hour/week), body mass index (< 23, 23 to < 25, or ≥ 25 kg/m^2), history of polyp resection (never, < 2, 2 to < 4, or ≥ 4 years), family history of colorectal cancer (yes or no), aspirin use (yes or no), hypertension (yes or no), diabetes (yes or no), dietary fiber intake (< 15, 15 to < 20, 20 to < 25, 25 to < 35, or ≥ 35 g/day), red/processed meat intake (g/day, continuous), and menopausal status (premenopausal or postmenopausal, applicable only for women).

*Proximal colon included cecum, ascending colon, and transverse colon, while distal colon/rectum included descending colon, sigmoid colon and rectum. Multiple location group included cases with adenomas in multiple anatomical sites within the colorectum.

†Advanced adenomas were defined as those with villous components, a diameter or ≥ 10 mm, or high-grade dysplasia.

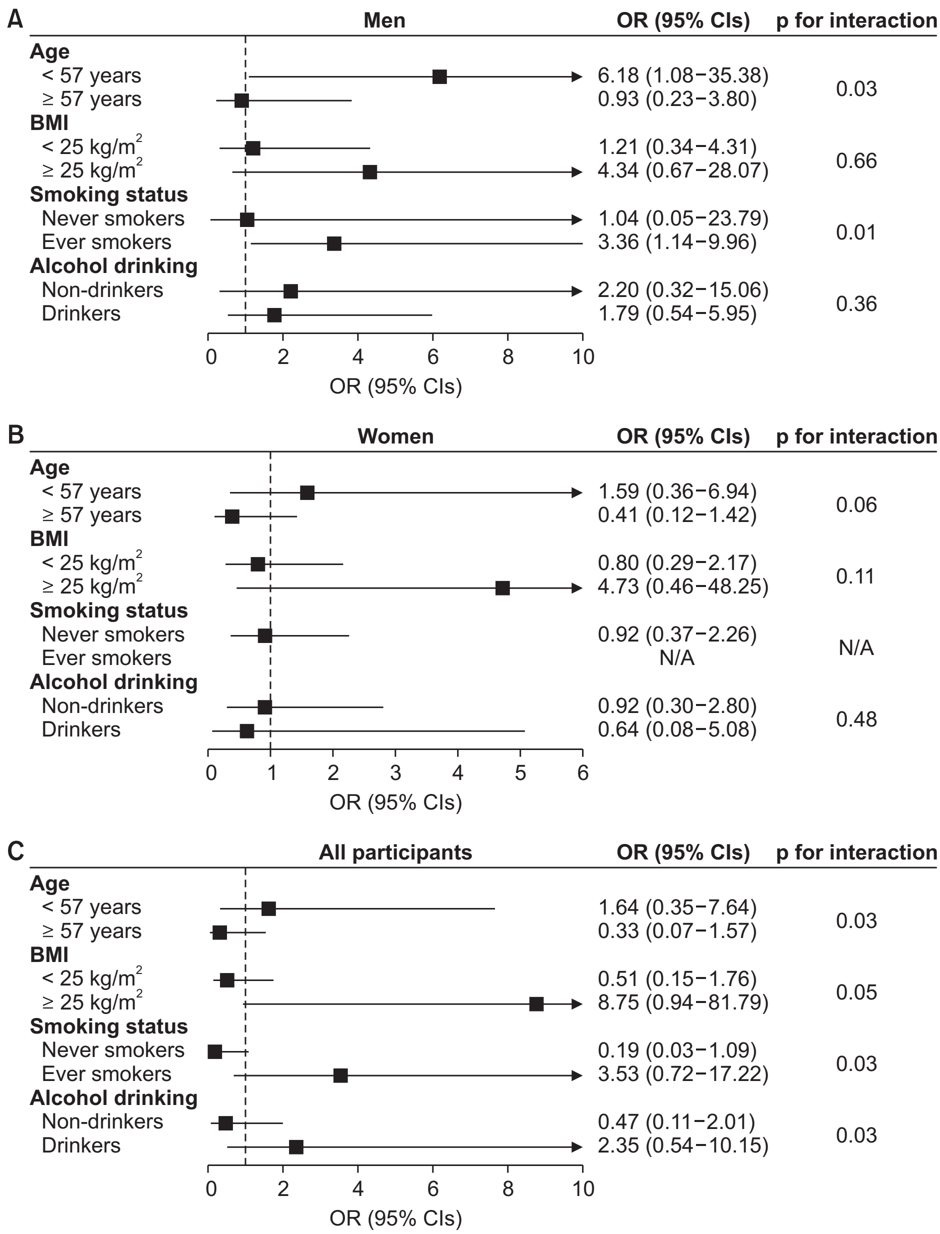

Fig. 1. Subgroup analysis for the associations between dietary calcium intake and colorectal adenoma among (A) men, (B) women, and (C) all participants by potential effect modifiers. Model was adjusted for age (years, continuous), gender (men or women, applicable only for all participants), alcohol consumption (men: none, < 40, 40 to < 90, 90 to < 170, 170 to < 320, or ≥ 320 g/day; women: none, < 20, 20 to < 100, or ≥ 100 g/day), smoking status (men: never, past smoker with pack-years missing, < 19.9 pack-years, ≥ 19.9 pack-years, current smokers with < 18.8 pack-years, or ≥ 18.8 pack-years; women: never or ever), education level (middle school or below, high school, or college or above), physical activity (none, 0 to < 15, or ≥ 15 METs-hour/week), BMI (< 23, 23 to < 25, or ≥ 25 kg/m^2), history of polyp resection (never, < 2, 2 to < 4, or ≥ 4 years), family history of colorectal cancer (yes or no), aspirin use (yes or no), hypertension (yes or no), diabetes (yes or no), dietary fiber intake (< 15, 15 to < 20, 20 to < 25, 25 to < 35, or ≥ 35 g/day), red/processed meat intake (g/day, continuous), and menopausal status (premenopausal or postmenopausal, applicable only for women). ORs for the highest vs. lowest group of dietary calcium intake were presented (< 350 mg/day vs. ≥ 600 mg/day for men, < 400 mg/day vs. ≥ 600 mg/day for women, and < 250 mg/day vs. ≥ 650 mg/day for all participants). Detailed information on ORs and 95% CIs is presented in Supplementary Table 5. BMI, body mass index; OR, odds ratio; CIs, confidence intervals; N/A, not applicable.

dietary calcium intake (p for trend = 0.41). When analyzing by adenoma status, a similar non-significant inverse association between dietary calcium intake and advanced adenoma was observed among men; the OR (95% CIs) was 2.47 (0.54–11.37) for < 300 mg/day compared to ≥ 600 mg/day of dietary calcium intake (p for trend = 0.25).

Subgroup analyses on the associations between dietary calcium intake and colorectal adenoma

We found a significant interaction by age in the association between dietary calcium intake and the prevalence of colorectal adenoma among men (Fig. 1, Supplementary Table 5). The ORs (95% CIs) were 6.18 (1.08–35.38) in the < 57 years group and 0.93 (0.23–3.80) in the ≥ 57 years group for < 350 mg/day, compared to ≥ 600 mg/day of dietary calcium intake (p for interaction = 0.03). Additionally, a potential interaction by smoking status was observed among men, where the ORs (95% CIs) were 1.04 (0.05–23.79) in never smokers and 3.36 (1.14–9.96) in ever smokers for < 350 mg/day, compared to ≥ 600 mg/day of dietary calcium intake (p for interaction = 0.01). Among women, however, there were no significant interactions by age, BMI, smoking status, and alcohol drinking. When including all participants, the associations between dietary calcium intake and the prevalence of colorectal adenoma were modified by age, BMI, smoking status, and alcohol drinking (p for interaction = 0.03 for age; 0.05 for BMI; 0.03 for smoking status; and 0.03 for alcohol drinking).

DISCUSSION

Our analysis revealed that low dietary calcium intake was associated with a higher prevalence of colorectal adenoma, particularly among men, with a suggestive inverse association observed among women. There were also suggestive inverse associations between lower dietary calcium intake and a higher prevalence of distal colon/rectal adenoma in women, as well as advanced adenoma in men. Among men, the association between low dietary calcium intake and a high prevalence of colorectal adenoma was modified by age and smoking status, with stronger inverse associations found in younger men and ever smokers.

Several epidemiologic studies have reported inverse associations between calcium intake and colorectal neoplasia. The meta-analysis including 8 prospective studies found that a 300 mg/day increase in total calcium intake was associated with a 5% reduction in the risk of colorectal adenoma [8]. Few studies have been conducted in Asian populations, yielding mixed findings. A cross-sectional study from Korea found a similar inverse association to ours between dietary calcium intake and colorectal adenoma, particularly among women, with an OR (95% CIs) of 0.44 (0.19–1.03) for the highest quartile [18]. Similarly, the Colorectal Adenoma Study in Tokyo reported that higher dietary calcium intake was associated with a lower prevalence of colorectal adenoma, with an OR (95% CIs) of 0.67 (0.47–0.95) for the highest quintile compared to the lowest [17]. However, the Takayama Study in Japan, a prospective study, did not find a significant association, with relative risks (RRs) (95% CIs) of 1.14 (0.77–1.69) for men and 1.16 (0.67–2.05) for women in the highest tertile compared to the lowest [19].

We observed a more pronounced association between dietary calcium intake and colorectal adenoma in men compared to women. This difference may result from the distinct distribution of dietary calcium intake by gender, with fewer women consuming extremely low levels. Our study also found potential inverse associations with distal colon/rectal adenoma in women. Previous studies have yielded mixed results: some prospective studies reported stronger inverse associations with distal colon or rectal cancer compared to proximal colon cancer [14,24], while one study found an association with proximal colon cancer [25], and another found no differences in associations by subsite [26]. Additionally, we identified a potential association between lower dietary calcium intake and a higher prevalence of advanced adenoma, consistent with a meta-analysis reporting an inverse association with advanced adenoma for a 300 mg/day increase in total calcium intake (summary RR [95% CIs]: 0.89 [0.85–0.94]) [8]. Further studies with larger populations are warranted to explore the association between dietary calcium intake and colorectal adenoma across various subsites and adenoma status.

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Age and smoking status were found to be effect modifiers among men, with significant inverse associations specifically observed in individuals younger than 57 years and among ever smokers. The stronger inverse association in the younger age group may be attributed to age-related differences in calcium absorption, as younger individuals may have more efficient calcium uptake [27]. This observation aligns with a case-control study from the US, which also reported stronger associations in individuals younger than 67 years compared to those 67 years or older. Additionally, the stronger inverse association specifically among ever smokers is consistent with findings from Health Professionals' Follow-up Study, which indicated a more pronounced protective effect of calcium intake in ever smokers compared to never smokers [28]. This result from our study may probably due to the small number of cases among never smokers, which shows a consistent result among ever smokers similar to that observed in men. Further studies are needed to elucidate the mechanisms behind this interaction.

Calcium has been hypothesized to have protective effects against the colorectal neoplasia. It is proposed to inhibit the development of colorectal neoplasia by binding to bile acids and free fatty acids, which irritate colon epithelial cells, forming insoluble calcium soaps [5]. Additionally, calcium intake may activate the calcium-sensing receptor, increasing intracellular calcium levels, thereby inducing effects that restrain cell growth and differentiation in transformed colon cells [6]. One mechanism through which this occurs is the promotion of E-cadherin expression by extracellular calcium, which helps the receptor strengthen cell-cell adhesion and reduces the potential for metastasis, contributing to the suppression of tumor growth in the colon [29].

A major strength of this study is that it was able to capture inverse associations between extremely low calcium intake and the prevalence of colorectal adenoma in a population with a relatively low dietary calcium intake, which had a median intake of 447 mg/day, compared to Western populations where the mean intake exceeds 800 mg/day [16]. Additionally, colorectal adenoma cases were confirmed via colonoscopy throughout the entire colon by gastroenterologists, allowing classification by location and ensuring objective case ascertainment. Furthermore, we used a multicenter approach, recruiting participants from eight centers across Korea. However, there were several limitations to this study. The cross-sectional design limited the establishment of causality between calcium intake and colorectal adenoma. Moreover, measurement error from dietary assessments may still be present. Residual confounding factors could not be completely ruled out.

In conclusion, this study found that lower dietary calcium intake was suggestively associated with a high prevalence of colorectal adenoma, particularly among men. Further studies are needed to replicate our study in other Asian populations.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Yun Jeong Lim, Hyun Jeong Cho, Jung Eun Lee. Data curation: Jioh Kang, Sang Hoon Kim, Joowon Chung, Dong Hyun Kim, Min Kyu Jung, Seun Ja Park, Hoon Jai Chun, Yun Jeong Lim, Hyun Jeong Cho, Jung Eun Lee. Formal analysis: Jioh Kang, Hyun Jeong Cho. Funding acquisition: Jung Eun Lee. Project administration: Yun Jeong Lim. Supervision: Yun Jeong Lim, Hyun Jeong Cho, Jung Eun Lee. Writing – original draft: Jioh Kang, Hyun Jeong Cho, Jung Eun Lee. Writing – review & editing: Jioh Kang, Sang Hoon Kim, Joowon Chung, Dong Hyun Kim, Min Kyu Jung, Seun Ja Park, Hoon Jai Chun, Yun Jeong

Lim, Hyun Jeong Cho, Jung Eun Lee.

ORCID

Jioh Kang, https://orcid.org/0009-0003-9035-9999
Sang Hoon Kim, https://orcid.org/0000-0003-3548-1986
Joowon Chung, https://orcid.org/0000-0003-1572-8056
Dong Hyun Kim, https://orcid.org/0000-0001-5778-1264
Min Kyu Jung, https://orcid.org/0000-0001-8749-408X
Seun Ja Park, https://orcid.org/0000-0003-3217-5115
Hoon Jai Chun, https://orcid.org/0000-0002-5539-361X
Yun Jeong Lim, https://orcid.org/0000-0002-3279-332X
Hyun Jeong Cho, https://orcid.org/0000-0003-0055-2334
Jung Eun Lee, https://orcid.org/0000-0003-1141-878X

SUPPLEMENTARY MATERIALS

Supplementary data is available at https://doi.org/10.52927/jdcr.2024.12.2.53.

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