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Original Article

Osteoporosis Is Associated with an Increased Risk of Colorectal Adenoma and High-Risk Adenoma: A Retrospective, Multicenter, Cross-Sectional, Case-Control Study

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Background/Aims: The protective effects of vitamin D and calcium on colorectal neoplasms are known. Bone mineral density (BMD) may be a reliable biomarker that reflects the long-term anticancer effect of vitamin D and calcium. This study aimed to evaluate the association between BMD and colorectal adenomas including high-risk adenoma.

Methods: A multicenter, cross-sectional, case-control study was conducted among participants with average risk of colorectal cancer who underwent BMD and screening colonoscopy between 2015 and 2019. The main outcome was the detection of colorectal neoplasms. The variable under consideration was low BMD (osteopenia/osteoporosis). The logistic regression model included baseline demographics, components of metabolic syndrome, fatty liver disease status, and aspirin and multivitamin use.

Results: A total of 2,109 subjects were enrolled. The mean age was 52.1±10.8 years and 42.6% were male. The adenoma detection rate was 43%. Colorectal adenoma and high-risk adenoma were both more prevalent in subjects with low BMD than those with normal BMD (48.2% vs 38.8% and 12.1% vs 9.1%). In the univariate analysis, old age, male sex, smoking, metabolic components, fatty liver, and osteoporosis were significantly associated with the risk of adenoma and high-risk adenoma. In the multivariate analysis, osteoporosis was independently associated with risk of colorectal adenoma (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.11 to 2.46; p=0.014) and high-risk adenoma (OR, 1.94; 95% CI, 1.14 to 3.29; p=0.014).

Conclusions: Osteoporosis is an independent risk factor of colorectal adenoma and high-risk adenoma. **(Gut Liver 2022;16:269-276)**

Key Words: Bone mineral density; Osteoporosis; Colorectal adenoma; High-risk adenoma

INTRODUCTION

Colorectal cancer (CRC) is a common and lethal cancer worldwide.[1] Genetic and environmental factors are associated with the likelihood of developing CRC. On the other hand, several factors such as specific diet have been reported by several studies to be associated with a decreased risk.

Vitamin D act as inhibitors of CRC by effects that influence both initiation and progression.[2] Observational studies have revealed a link between poor vitamin D status and the risk of many cancers, including CRC.[3] Vitamin D has also been proven to have anticancer effects against CRC by several clinical trials and literature reviews.[4-8] Meanwhile, because colorectal adenoma is an obvious precursor of CRC, known as the adenoma-carcinoma sequence,[9] vitamin D is expected to be associated with the risk of

colorectal adenomas as well as CRC. However, a recently published randomized controlled trial failed to show a significant relationship between vitamin D and colorectal adenoma risk.[10] Therefore, whether vitamin D is linked to the risk of colorectal adenomas is unproven.

Another dietary protective factor is the intake of calcium supplementation. Three controlled studies evaluated the efficacy of supplemental calcium for prevention of colorectal adenomas. A meta-analysis including a total of 1,485 subjects showed that the risk of colorectal adenoma was significantly lower in patients with intake of calcium.[11] Despite these benefits in adenoma prevention, whether calcium supplementation reduces the risk of CRC is still debatable.

The circulating form of vitamin D in the body is 25(OH)D. Serum 25(OH)D concentration has a relatively short half-life of 2 to 3 weeks and depends on sunlight exposure and dietary intake.[12] Therefore, using serum 25(OH)D level as a criterion for the anticancer effect of vitamin D on colorectal neoplasms may not be appropriate. Instead, bone mineral density (BMD) reflects the effect of vitamin D and calcium over several months to years, and may therefore be a more reliable biomarker that could reflect the anticancer effect of vitamin D and calcium. Indeed, several prospective cohort studies have shown that high BMD has a protective effect against CRC.[4,13] However, it is unclear whether there is an association between low BMD and risk of colorectal adenomas or high-risk colorectal neoplasms. To date, only a few small-scale studies conducted at single centers have been reported.[14-16] However, these studies used small sample size and did not show the increased risk of high-risk adenoma. This study aimed to confirm the association between BMD and the occurrence of colorectal adenomas including high-risk colorectal neoplasms and utilized large-scale health check-up databases to analyze various clinical and metabolic factors.

MATERIALS AND METHODS

1. Study design

This multicenter cross-sectional study included consecutive subjects who participated in voluntary health screening programs at four teaching hospitals (Dongguk University Ilsan Hospital, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University Hospital, and National Cancer Center) in South Korea between January 2015 and December 2019. Asymptomatic participants who underwent screening colonoscopy and concurrently performed bone densitometry (dual-energy X-ray absorptiometry) for routine health check-ups were eligible for the study. Participants who underwent colonoscopy for any symptoms or therapeutic purposes, incomplete colonoscopy due to non-cooperation or inadequate preparation, and previous colonic examination by colonoscopy or barium enema in the previous 10 years were not eligible. Among the eligible subjects, those with a previous history of colorectal resection and insufficient clinical information were excluded. Information regarding underlying diseases or medical history was obtained using questionnaires established from the screening programs. Laboratory findings were reviewed from the medical records. The study was approved by the institutional review board of each participating institution (IRB No. 2021-02-019). For this type of study, formal consent is not required.

2. Endoscopy and pathology

All enrolled subjects were examined by experienced endoscopists with video colonoscopy (Olympus CF-H260 or CF-Q260; Olympus Optical Co., Ltd., Tokyo, Japan). Intravenous midazolam (Midazolam; Bukwang Pharm Co., Ltd., Seoul, Korea) was administered to subjects who preferred conscious sedation. The dose of midazolam was determined according to a unified protocol based on the subject's age and weight. Opioids such as meperidine or fentanyl were routinely used as analgesics. Bowel cleansing was achieved using polyethylene glycol plus ascorbic acid (Coolprep; Taejoon Pharm. Co., Seoul, Korea) or an oral sulfate solution (Innofree; MH Healthcare, Seoul, Korea). During endoscopic examination, tissue specimens from biopsy or polypectomy were obtained for histological evaluation at the sites of lesions suspected to be benign or malignant neoplasms. High-risk colorectal adenoma was determined as advanced colorectal neoplasia or 3 or more colorectal adenomas. Advanced neoplasia was defined if the lesion had one or more features of the followings: (1) largest diameter ≥10 mm; (2) including tubulovillous or villous histology confirmed; or (3) including high grade dysplasia or invasive cancer confirmed by pathologic exam.[17] Sessile serrated lesion, traditional serrated adenoma, and hyperplastic polyp ≥10 mm were investigated, and these lesions were also regarded as colon neoplasia. In cases of multiple lesions, the most advanced pathology was selected as the definitive lesion. Nonspecific inflammation or hyperplastic lesions such as hyperplastic polyp <10 mm was classified as normal.

3. Bone mass density

BMD was measured using bone densitometry (Horizon DXA system, Hologic, Inc., Marlborough, MA, USA) by either the Z-score or the T-score based on the age 50, ac-

cording to the World Health Organization criteria.[18] For those aged <50 years, a Z-score of ≤–2.0 was considered below the expected range for age, indicating low BMD. Z-scores >–1.9, were considered normal BMD for the same age group. For those ≥50 years of age, T-scores were categorized into three groups (≥–1.0, –1.1 to –2.4, and ≤–2.5). Osteoporosis was defined as a reduction of more than 2.5 standard deviations (T-score ≤–2.5) of bone mass at the spine or total hip. T-scores ≥–1.0 and –1.1 to –2.4 were classified into normal and decreased bone density (osteopenia), respectively. Osteopenia or osteoporosis was considered low BMD.

4. Definitions and exposure measurements

Current smoker was defined as smoking more than 1 cigarette regularly during the recent 1 year. Alcohol drinking meant drinking >140 g alcohol per week. Hypertension meant ≥140/90 mm Hg or taking antihypertensives. Diabetes meant a fasting plasma glucose concentration of ≥126 mg/dL or taking anti-diabetic drugs. Other metabolic components were included; high triglycerides (≥150 mg/dL), low high-density lipoprotein cholesterol (male: <40 mg/dL, female: <50 mg/dL), and high waist circumference (male: ≥90 cm, female: ≥80 cm).[19] In addition, the presence of fatty liver on ultrasound and the use of aspirin and vitamin supplements were included in the analysis as covariates.

5. Statistical analysis

The primary outcome of this study was to determine whether the incidence of colorectal adenomas and high-risk adenoma differs between the group with low BMD and those with normal BMD. Baseline and clinical characteristics between the normal and low BMD groups were compared by sex using the independent sample t-tests or the Pearson chi-square tests. Logistic regression analyses using odds ratios (ORs) and 95% confidence intervals (CIs) were performed to identify factors associated with the occurrence of colorectal adenomas. The multivariate regression model included covariates with p-values <0.1, in the univariate analyses. Multivariate regression was also performed in subgroups based on sex. The association of advanced neoplasia, high-risk adenoma or serrated polyps with BMD findings was also evaluated. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS Statistics (version 21.0; IBM Corp., Armonk, NY, USA).

RESULTS

1. Study participants and characteristics

Of the 2,318 eligible subjects during the study period, 209 were excluded from the study for the following reasons: previous colorectal resection (n=17) and inadequate information (n=192) (Fig. 1). The mean age of the 2,109 enrolled subjects was 52.1±10.8 years (range, 29 to 87 years), and 899 (42.6%) were male. The adenoma detection rate was 43% (906/2,109). High-risk adenoma and serrated polyps were observed in 220 (10.4%) and 114 (5.4%) subjects, respectively. Low BMD was observed in 44.1% (931/2,109) of the subjects, which was significantly different between men (n=274, 30.5%) and women (n=657, 54.3%) (p<0.001).

Osteoporosis was observed in 6.6%. Osteopenia was observed in 37.6%. Increased age and colorectal adenomas were significantly associated with low BMD in both men and women (Table 1). Conversely, vitamin supplements exhibited a reverse association with abnormal BMD in both sexes. In addition, diabetes, hypertension, low high-density lipoprotein, and fatty liver were found to be related to low BMD in females, but not in males.

2. Low BMD and colorectal adenoma

In the univariate analysis, age ≥50 years, male, and current smokers were associated with the risk of adenoma, whereas drinking habits were not (Table 2). Metabolic disease-related underlying disorders, fatty liver, and low BMD were also associated with increased incidence of colorectal adenoma. In patients diagnosed with colorectal adenoma,

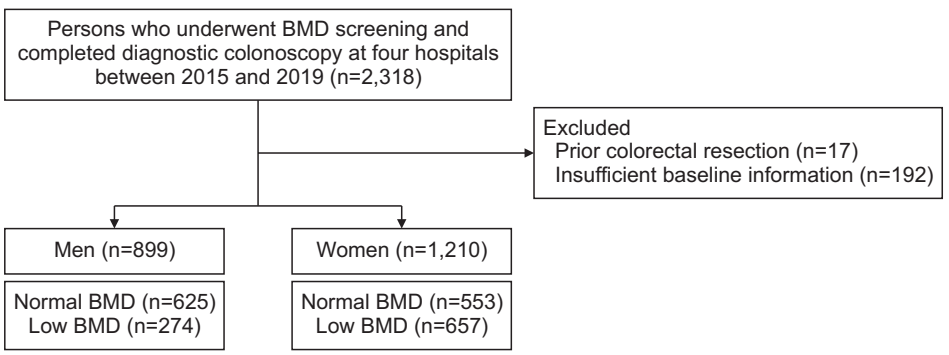

Fig. 1. Flow diagram illustrating selection of the study population.
BMD, bone mineral density.

Table 1. Baseline Characteristics Based on BMD by Sex

Variable	Total (n=2,109)	Men (n=899)			Women (n=1,210)		
		Normal BMD (n=625)	Low BMD (n=274)	p-value	Normal BMD (n=553)	Low BMD (n=657)	p-value
Age, yr	52.1±10.8	49.6±10.7	56.7±10.6	<0.001	46.9±8.5	57.0±9.8	<0.001
Current smoker	391 (18.5)	248 (39.7)	101 (36.9)	0.425	21 (3.8)	21 (3.2)	0.569
Drinking	1,114 (52.8)	442 (70.7)	194 (70.8)	0.980	280 (50.6)	198 (30.1)	<0.001
TG, mg/dL	105.9±70.7	129.7±84.4	129.4±83.2	0.958	85.6±50.4	90.4±53.7	0.115
HDL, mg/dL	57.7±14.9	51.3±12.5	51.6±12.6	0.743	63.8±14.9	61.3±14.8	0.004
WC, cm	84.2±8.9	88.3±8.7	86.2±7.9	0.001	81.1±8.6	82.0±8.0	0.057
Hypertension	429 (20.3)	152 (24.3)	71 (25.9)	0.611	57 (10.3)	149 (22.7)	<0.001
Diabetes mellitus	185 (8.8)	77 (12.3)	36 (13.1)	0.733	13 (2.4)	59 (9.0)	<0.001
Fatty liver	796 (37.7)	341 (54.6)	127 (46.4)	0.023	123 (22.2)	205 (31.2)	<0.001
Aspirin	110 (5.2)	41 (6.6)	28 (10.2)	0.058	7 (1.3)	34 (5.2)	<0.001
Multivitamin	201 (9.5)	57 (9.1)	13 (4.7)	0.024	76 (13.7)	55 (8.4)	0.003
Colorectal neoplasms							
Adenoma	906 (43.0)	317 (50.7)	194 (70.8)	<0.001	140 (25.3)	255 (38.8)	<0.001
3 or more adenoma	159 (7.5)	60 (9.6)	46 (16.8)	0.002	15 (2.7)	38 (5.8)	0.009
Adenoma ≥10 mm	70 (3.3)	23 (3.7)	16 (5.8)	0.143	10 (1.8)	21 (3.2)	0.128
Advanced neoplasia	85 (4.0)	30 (4.8)	20 (7.3)	0.132	12 (2.2)	23 (3.5)	0.169
High-risk adenoma	220 (10.4)	83 (13.3)	57 (20.8)	0.004	24 (4.3)	56 (8.5)	0.004
SSL, TSA, or HP ≥10 mm	114 (5.4)	32 (5.1)	12 (4.4)	0.636	38 (6.9)	32 (4.9)	0.137

Data are presented as mean±SD or number (%).
BMD, bone mineral density; TG, triglyceride; HDL, high-density lipoprotein cholesterol; WC, waist circumference; SSL, sessile serrated lesion; TSA, traditional serrated adenoma; HP, hyperplastic polyp.

Table 2. Factors Associated with Incidence of Colorectal Adenoma

Factor	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age ≥50 yr	3.70 (3.06–4.46)	<0.001	3.71 (2.94–4.68)	<0.001
Male sex	2.72 (2.27–3.25)	<0.001	2.88 (2.28–3.64)	<0.001
Current smoker	2.04 (1.63–2.55)	<0.001	1.60 (1.21–2.11)	0.001
Drinking	1.05 (0.88–1.25)	0.570		
High TG	1.48 (1.18–1.85)	0.001	0.99 (0.75–1.30)	0.939
Low HDL	1.33 (1.06–1.66)	0.014	1.03 (0.79–1.33)	0.844
High WC	1.50 (1.25–1.79)	<0.001	1.17 (0.94–1.45)	0.157
Hypertension	2.62 (2.11–3.26)	<0.001	1.55 (1.20–1.99)	0.001
Diabetes mellitus	2.41 (1.77–3.30)	<0.001	1.16 (0.82–1.65)	0.389
Fatty liver	1.85 (1.55–2.22)	<0.001	1.15 (0.92–1.44)	0.221
Aspirin	0.48 (0.32–0.71)	<0.001	0.75 (0.48–1.15)	0.186
Multivitamin	0.43 (0.31–0.60)	<0.001	0.60 (0.42–0.86)	0.005
BMD, normal	Reference		Reference	
Osteopenia	1.37 (1.14–1.64)	0.001	1.21 (0.97–1.51)	0.092
Osteoporosis	2.20 (1.54–3.15)	<0.001	1.65 (1.11–2.46)	0.014

OR, odds ratio; CI, confidence interval; TG, triglyceride; HDL, high-density lipoprotein cholesterol; WC, waist circumference; BMD, bone mineral density.

aspirin administration and vitamin supplementation were significantly lower. In the multivariate analysis, colorectal adenoma was significantly higher with increased age, male sex, current smoking status, hypertension, and osteoporosis (OR, 1.65; 95% CI, 1.11 to 2.46; p=0.014) (Table 2). The use of vitamin supplements was lower in patients diagnosed with colorectal adenoma, whereas other metabolic components, fatty liver, and aspirin were not associated with adenoma detection.

3. Low BMD and high-risk adenoma

In the multivariate analyses, age ≥50 years, male, current smokers, high waist circumference, hypertension, and osteoporosis (OR, 1.94; 95% CI, 1.14 to 3.29; p=0.014) were associated with high-risk adenoma (Table 3). The ORs for the detection of multiple adenomas (3 or more) and advanced neoplasia in patients with osteoporosis were 2.05 (p=0.016) and 1.92 (p=0.133), respectively (Table 4). These ORs for the detection of colorectal adenomas were consistently high in patients with osteoporosis compared to those with osteopenia.

Table 3. Factors Associated with Incidence of High-Risk Adenoma

Factor	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age ≥50 yr	3.82 (2.67–5.46)	<0.001	3.56 (2.38–5.31)	<0.001
Male sex	2.61 (1.95–3.48)	<0.001	2.38 (1.68–3.39)	<0.001
Current smoker	2.22 (1.63–3.03)	<0.001	1.91 (1.33–2.75)	0.001
Drinking	1.15 (0.87–1.52)	0.333		
High TG	1.29 (0.91–1.83)	0.148		
Low HDL	1.25 (0.88–1.77)	0.208		
High WC	1.63 (1.23–2.16)	0.001	1.43 (1.04–1.96)	0.029
Hypertension	2.35 (1.74–3.18)	<0.001	1.41 (1.00–1.98)	0.051
Diabetes mellitus	1.93 (1.28–2.91)	0.002	0.99 (0.64–1.55)	0.967
Fatty liver	1.65 (1.25–2.18)	<0.001	1.04 (0.75–1.44)	0.813
Aspirin	0.36 (1.70–4.35)	<0.001	1.27 (0.77–2.12)	0.350
Multivitamin	0.57 (0.22–1.02)	0.056	0.87 (0.47–1.60)	0.656
BMD, normal	Reference		Reference	
Osteopenia	1.25 (0.93–1.69)	0.140	1.18 (0.85–1.65)	0.322
Osteoporosis	2.20 (1.36–3.53)	0.001	1.94 (1.14–3.29)	0.014

OR, odds ratio; CI, confidence interval; TG, triglyceride; HDL, high-density lipoprotein cholesterol; WC, waist circumference; BMD, bone mineral density.

Table 4. Association between BMD and Colorectal Neoplasms by Multivariate Logistic Regression Analysis

Variable	Normal BMD (n=1,178), No. (%)	Osteopenia (n=792)			Osteoporosis (n=139)		
		No. (%)	Adjusted OR (95% CI)	p-value	No. (%)	Adjusted OR (95% CI)	p-value
Adenoma	457 (38.8)	368 (46.5)	1.21 (0.97–1.51)	0.092	81 (58.3)	1.65 (1.11–2.46)	0.014
3 or more adenoma	75 (6.4)	64 (8.1)	1.17 (0.80–1.72)	0.423	20 (14.4)	2.05 (1.14–3.69)	0.016
Advanced neoplasia*	42 (3.6)	35 (4.4)	1.41 (0.85–2.32)	0.183	8 (5.8)	1.92 (0.82–4.49)	0.133
High-risk adenoma†	107 (9.1)	88 (11.1)	1.18 (0.85–1.65)	0.322	25 (18.0)	1.94 (1.14–3.29)	0.014
SSL, TSA, or HP ≥10 mm	70 (5.9)	36 (4.5)	0.80 (0.53–1.21)	0.293	8 (5.8)	1.04 (0.49–2.22)	0.921

Other covariates with p-values <0.1 in the univariate analyses were adjusted in the multivariate analyses.
BMD, bone mineral density; OR, odds ratio; CI, confidence interval; SSL, sessile serrated lesion; TSA, traditional serrated adenoma; HP, hyperplastic polyp.
*Advanced neoplasia was defined as (1) largest diameter ≥10 mm, (2) confirmed tubulovillous or villous histology, and (3) high grade dysplasia or invasive colorectal cancer; †High-risk adenoma was defined as (1) advanced neoplasia and (2) the presence of 3 or more adenomas.

Table 5. Adjusted Odds Ratios for the Detection of Adenoma and High-Risk Adenoma: Subgroup Analyses by Sex

BMD		Men (n=899)			Women (n=1,210)		
		No./No. (%)	Adjusted OR (95% CI)	p-value	No./No. (%)	Adjusted OR (95% CI)	p-value
Adenoma	BMD						
	Normal	317/625 (50.7)	Reference		140/553 (25.3)	Reference	
	Osteopenia	171/244 (70.1)	1.46 (1.03–2.08)	0.035	197/548 (35.9)	1.07 (0.80–1.44)	0.634
	Osteoporosis	23/30 (76.7)	1.45 (0.59-3.56)	0.417	58/109 (53.2)	1.66 (1.04-2.65)	0.034
High-risk adenoma*	BMD						
	Normal	83/625 (13.3)	Reference		24/553 (4.3)	Reference	
	Osteopenia	48/244 (19.7)	1.20 (0.79–1.83)	0.346	40/548 (7.3)	1.02 (0.58–1.79)	0.941
	Osteoporosis	9/30 (30.0)	1.76 (0.75–4.10)	0.193	16/109 (14.7)	1.70 (0.82–3.55)	0.157

Other covariates with p-values <0.1 in the univariate analyses were adjusted in the multivariate analyses.
BMD, bone mineral density; OR, odds ratio; CI, confidence interval.
*High-risk adenoma was defined as (1) advanced colorectal neoplasia (adenomas ≥10 mm, tubulovillous or villous histology, high grade dysplasia or invasive colorectal cancer) and (2) the presence of 3 or more colorectal adenomas.

4. Low BMD and serrated polyp

The detection of serrated polyps was not associated with osteoporosis, with OR of 1.04 (95% CI, 0.49 to 2.22; p=0.921).

5. Subgroup analyses

In the subgroup analyses by sex, adjusted ORs for the detection of adenoma and high-risk adenoma tended to increase from patients with normal BMD to those with

osteoporosis (Table 5). Adjusted ORs for the detection of adenoma and high-risk adenoma were 1.45 and 1.76 in men with osteoporosis, even though statistical significance was lacked. The risk of adenoma and osteoporosis was significantly associated in the subgroup of women (OR, 1.66; 95% CI, 1.04 to 2.65; p=0.034). The adjusted OR for the detection of high-risk adenoma was 1.70 (p=0.157) in women with osteoporosis.

DISCUSSION

We conducted a multicenter study using health check-up data to evaluate the association between osteoporosis and colorectal adenoma including high-risk adenoma. Increased age, male sex, smoking, hypertension, and low BMD were associated with higher colorectal adenoma risk, whereas vitamin supplementation showed a protective effect on the risk of colorectal adenoma. Further, osteoporosis was at increased risk of multiple (3 or more) or high-risk adenomas. To the best of our knowledge, this is the first study showing a positive correlation between low BMD and high-risk adenoma. The findings of subgroup by sex showed similar outcomes in terms of the adjusted ORs for the association between osteoporosis and adenoma risks. However, statistical significance has been demonstrated only in women with osteoporosis for the risk of colorectal adenoma, maybe, due to the limited sample size. Further large-scale studies may improve the statistical power. Maintaining adequate bone density may be a meaningful factor in preventing colorectal adenomas, particularly in women. No statistical significance was observed in the association between serrated polyps and BMD, but additional studies with larger cohorts are required in the future.

From the studies to date, the effect of 25(OH)D concentration or vitamin D supplementation on colorectal adenoma seems to be equivocal.[20,21] In the present study, the detection rate of colorectal adenoma was significantly higher in women with osteoporosis than in those with normal BMD, which is in agreement with the results of previous observational studies.[14,16] The reason why low BMD is associated with colorectal adenoma detection, particularly in women, is perhaps because bone density is an indicator that reflects estrogen exposure as well as vitamin D. NHANES cohort studies have reported that BMD is associated with cancers of the uterus and breast in addition to CRC as an indicator of estrogen exposure.[13]

Bone mass is positively associated with serum 25(OH)D and calcium intake, but negatively correlated with $1,25(OH)_2D$, which increases as a compensatory action when calcium intake decreases.[22] The 25(OH)D concentration represents the endogenous vitamin D status and bone density. However, 25(OH)D has a relatively short half-life and is not consistent with dietary factors; therefore, BMD may better represent long-term vitamin D status than serum 25(OH)D concentrations. It has been recently reported that the association between serum 25(OH)D concentration and BMD is inconsistent.[23] Another study reported that there was no relationship between vitamin D supplementation and CRC risk.[24,25] Although the anticancer effect of vitamin D on CRC is evident,[26-28] the role of vitamin D levels in predicting the risk of colorectal neoplasia is controversial. These findings suggest that BMD may be a reliable marker of long-term vitamin D status and calcium intake.

Our study is significant compared to previous studies in that it was a multicenter study involving a relatively large cohort and stratified by sex, and various metabolic components were included. In addition, we focused on high-risk adenomas, including multiple or large adenoma, and advanced colorectal neoplasia. Interestingly, the ORs for detection of high-risk adenomas were consistently higher than the ORs for detection of colorectal adenomas. Even though it lacks significance in this regard, more large-scale studies could support the present study. As a multicenter study, one concern is that the criteria and interpretation of BMD may differ among institutions. Fortunately, all institutions assessed BMD using dual-energy X-ray absorptiometry, which is a widely available and feasible technique as the gold standard.[18] Accordingly, the unified criteria based on the World Health Organization standard were applied to the BMD interpretation, thereby minimizing the variation among institutions. The application of T-scores to women is generally based on menopause. However, because it is difficult to accurately determine whether an individual has menopause, it is reasonable to interpret BMD differently based on the age 50 to evaluate the risk of fracture.[29]

There were also several weak points in this study. Firstly, because it was a retrospective, cross-sectional study, the temporal association and causality between osteoporosis and colorectal adenoma could not be evaluated. Secondly, age is one of the well-known risk factors for colorectal adenoma or cancer. Although the analysis was adjusted for age, there is a possibility of selection bias due to insufficient correction for age. Thirdly, we could not investigate the mechanism how osteoporosis is associated with colorectal adenoma and high-risk adenoma. Lastly, the data related to menopausal hormone replacement, bisphosphonate therapy, calcium supplementation, and serum vitamin D level were not included in the analyses. Since these factors

have a direct impact on the results of BMD, it is appropriate that they not be included in studies where BMD is an independent variable. However, previous studies have indicated that the use of oral bisphosphonates or calcium is associated with a reduced risk of CRC.[30-32] Therefore, it remains unclear whether the influence of these factors on colorectal adenoma can be completely neglected, and statistical considerations may be required. In addition, it would be interesting to compare whether BMD is associated with colorectal adenoma because BMD reflects vitamin D status or if it is more related to BMD itself, the result of several factors such as estrogen.

In conclusion, osteoporosis was found to be an independent risk factor of colorectal adenoma and high-risk adenoma. So, maintaining adequate BMD may prevent colorectal neoplasia including high-risk adenomas, in addition to the classical benefit of preventing fractures. In addition, subjects with low BMD should be screened for colorectal neoplasia adequately. Further large-scale prospective cohort studies are warranted to validate these findings.

CONFLICTS OF INTEREST

J.W.K. and J.P.I are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Study design: H.W.K. Data collection: J.H.N., M.K., D.J.O., K.H.R., S.J.K., J.P.I. Data analysis: H.W.K., J.H.N., M.K., K.H.R. Investigation: J.H.N., H.W.K., D.S.L., S.H.K. Methodology: H.W.K., J.B.J., J.W.K. Drafting of manuscript: J.H.N., H.W.K., D.K.J. Critical Revision: J.W.K., K.L.L., Y.J.L., J.P.I., J.S.K. All authors read and approved the final manuscript.

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