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Prognostic significance of osteopenia in patients with colorectal cancer: A retrospective cohort study

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Abstract

Aim: We examined the prognostic impact of osteopenia on the long-term outcomes of patients with colorectal cancer after laparoscopic colectomy along with other nutritional factors, including sarcopenia or the Glasgow Prognostic Score.

Methods: This retrospective cohort study analyzed the data of 230 patients with stage I–III colorectal cancers who underwent surgical resection between November 2010 and December 2015. Osteopenia and sarcopenia were evaluated by measuring the average pixel density in the mid-vertebral core of the 11th thoracic vertebra on enhanced computed tomography and the psoas muscle mass area at the third lumbar vertebra, respectively. The overall survival and disease-free survival rates were analyzed using Cox proportional hazards model and Kaplan–Meier curves with the log-rank test.

Results: Osteopenia was identified in 43 patients (18.7%). Univariate analysis showed that the disease-free survival rate was significantly worse in patients with stage II–III cancers, vascular invasion, carcinoembryonic antigen (CA) >5.0 ng/mL, CA19-9 > 37.0 U/mL, sarcopenia, and osteopenia (all $P < .01$). Multivariate analysis revealed that stage II–III cancers ($P = .01$), vascular invasion ($P = .01$), carcinoembryonic antigen >5.0 ($P < .01$), and osteopenia ($P < .01$) were significant independent disease-free survival predictors. In univariate analysis, the overall survival rate significantly decreased in patients with stage II–III cancers ($P = .03$), carcinoembryonic antigen >5.0 ($P < .01$), CA19-9 > 37.0 ($P < .01$), sarcopenia ($P < .01$), and osteopenia ($P < .01$). Multivariate analysis indicated that carcinoembryonic antigen >5.0 ($P = .04$), CA19-9 > 37.0 ($P = .05$), and osteopenia ($P < .01$) were significant independent predictors of overall survival.

Conclusion: Preoperative osteopenia could be a strong predictor of long-term outcomes in patients undergoing resection for colorectal cancer.

KEYWORDS

bone density, disease-free survival, osteopenia, sarcopenia, survival analysis

1 | INTRODUCTION

Colorectal cancer (CRC) ranks as the third most commonly diagnosed cancer and the second most frequent etiology of cancer-related mortality worldwide. The decline in the CRC mortality rate through the 2000s is attributed to improvements in treatment, changing patterns in CRC risk factors, and early screening; however, the mortality rate remains high.[1]

Recently, the association between sarcopenia and the prognosis of many malignant diseases, including CRC, has been emphasized.[2] Sarcopenia is defined as a decline in skeletal muscle mass and strength caused by aging, lack of activity, and chronic diseases, including various malignancies.[3] Several previous reported mechanisms can explain the associations between low skeletal muscle mass (ie, sarcopenia) and poor pathophysiological clinical outcome. Low skeletal muscle mass contributes to high systemic inflammation, reduced myokine production, and lower mitochondrial function. Furthermore, low skeletal muscle mass leads to an impairment in glucose clearance and tolerance and an alteration in the pharmacokinetics of chemotherapeutic drugs. These factors play an important role in cancer progression and poor response to treatment.[4]

Low skeletal muscle mass is strongly associated with bone mineral density (BMD) loss, which is osteopenia, suggesting that a lower muscle mass decreases the site-specific effect of skeletal loading, leading to reduced bone formation.[5] Many factors, such as heredity, mechanical stress, inflammation, and nutrition, affect the muscle and bone simultaneously; moreover, hormonal factors, including growth hormone, androgen, and vitamin D are also involved in the pathophysiology.[5] The association between endogenous sex hormones or vitamin D and prognosis of patients with CRC has already been reported.[6,7] However, the impact of osteopenia on the prognosis of patients with CRC remains unclear.

The present study aimed to investigate the prognostic impact of osteopenia on the long-term outcomes of patients with CRC after laparoscopic colectomy along with other nutritional factors, including sarcopenia or the Glasgow Prognostic Score (GPS).

2 | PATIENTS AND METHODS

This was a retrospective cohort study of 230 patients who underwent surgical resection for CRC at the International University of Health and Welfare Hospital (Nasushiobara, Tochigi Prefecture, Japan) between November 2010 and December 2015. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the International University of Health and Welfare Hospital (approval no: 20-B-451). All data were subject to strict privacy policies, and the patients or their family members had the option to drop out of the study at any time. The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and anonymized data.

A maintained database of patients with CRC was retrospectively reviewed; the primary endpoint was the death of patients with CRC after surgery. The inclusion criteria were as follows: (a) patients with CRC who underwent laparoscopic colorectal resection; (b) enhanced abdominal computed tomography (CT) performed within 30 d before surgery; and (c) complete follow-up data and clinical details. Patients who had (1) perioperative death (n = 1), (2) stage 0 or IV CRC (n = 19), (3) appendiceal and anal carcinoma (n = 1), (4) multiple cancers (n = 1), or (5) and underwent emergency surgery (n = 3), were excluded.

2.1 | Treatment and patient management

The Japanese Society for Cancer of the Colon and Rectum guidelines 2019[8] were used for surgical indications, surgical treatment, and chemotherapy selection for CRC, while the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (3rd English Edition)[9] was used for staging and pathological diagnosis.

Surgical resection included laparoscopic ileocecal resection, right or left hemi-colectomy, transverse colectomy, sigmoid colectomy, rectal anterior resection, abdominoperineal resection, and intersphincteric resection. The basic surveillance[8] after surgery was performed using tumor markers every 3 mo, while chest and abdominal enhanced CT and colonoscopy were performed every 6 mo and every 1 or 2 y, respectively.

A right-sided CRC was defined as that located in the cecum, ascending, and transverse colon, while that located within the splenic flexure and beyond was defined as left-sided CRC.[10] CRC recurrence after the primary operation was defined as newly detected local or distant metastatic tumors on enhanced CT or positron emission tomography with CT, with or without increased serum carcinoembryonic antigen or carbohydrate antigen 19-9 levels. Postoperative complications including anastomotic leakage, surgical site infection, ileus, and intraperitoneal abscess were defined as grade III or higher according to the Clavien–Dindo classification, which occurred within 30 d after surgery. All complications were defined as at least either one of those occurring within 30 d after surgery.

2.2 | Data collection

Clinicopathological data included sex, age, body mass index (BMI), comorbidities, complications, pre- and postoperative chemoradiotherapy, recurrent tumor resection, tumor-node-metastasis stage, tumor location, pathological type, survival duration, as well as preoperative serum albumin, C-reactive protein, calcium, carcinoembryonic antigen, and carbohydrate antigen 19-9 levels. The cutoff values for carcinoembryonic antigen and carbohydrate antigen 19-9 were set at the level of the upper normal limit. The systemic cumulative inflammation-based prognostic scoring system utilized in our study was the GPS, based on the combination of the C-reactive protein and serum albumin levels. Thus, the GPS was defined based on the presence of hypoalbuminemia (<3.5 mg/dL) and elevated C-reactive protein levels (>10 mg/L): in cases

where both levels were abnormal, the score was 2; if one level was abnormal, the score was 1; if neither level was abnormal, the score was 0.[11]

2.3 | Definition of osteopenia and sarcopenia

Osteopenia was defined as a decrease in BMD below the standard values, which was evaluated based on the results of a previous study as follows[12]: (men = [308.82–2.49 × age]; women = [311.84–2.41 × age]). By placing elliptical regions of interest in the mid-vertebral core of the 11th thoracic vertebra on preoperative enhanced CT,[13] we calculated the average pixel density of the trabecular bone to analyze BMD (Figure 1). The sizes of the regions of interest were constant in all patients (area: 200 mm^2) and were manually positioned according to the patients' morphology.

Sarcopenia was defined as a psoas muscle mass area (PMA) at the third lumbar vertebra below the sex-specific median size, calculated as follows: length of the major axes × the length of the minor axes × π (Figure 2).[14]

2.4 | Statistical analysis

The Mann–Whitney *U* and the chi-squared test were used to compare the continuous and dichotomous variables, respectively. Univariate and multivariate analyses of the disease-free survival (DFS) and overall survival (OS) rates were performed using the Cox proportional hazards model. The effects of osteopenia and sarcopenia on the risk of recurrence and death were estimated using the Kaplan–Meier curves with the log-rank test. STATA/IC v. 16.0 (STATA Statistical Software; StataCorp, College Station, TX) was used for statistical analysis. The level of significance was set at $P < .05$.

3 | RESULTS

3.1 | Patient characteristics

Table 1 shows the patient characteristics and the association between the clinical variables and osteopenia.

The median age was 67 (range: 32–89) y. The study included 136 men and 94 women. Pathological diagnosis of CRC showed that 73, 65, and 92 patients had stage I, II, or III cancers, respectively. There were 68 right-sided colon cancers, 61 left-sided colon cancers, and 101 rectal cancers.

The median BMDs were 230.4 and 190.2 Hounsfield units (HU) in men and women, respectively; 43 patients (18.7%) were classified to have osteopenia. The median PMAs were 26.1 and 13.6 cm^2 for men and women, respectively; sarcopenia was diagnosed in 114 patients (49.6%). Postoperative anastomotic leakage, surgical site

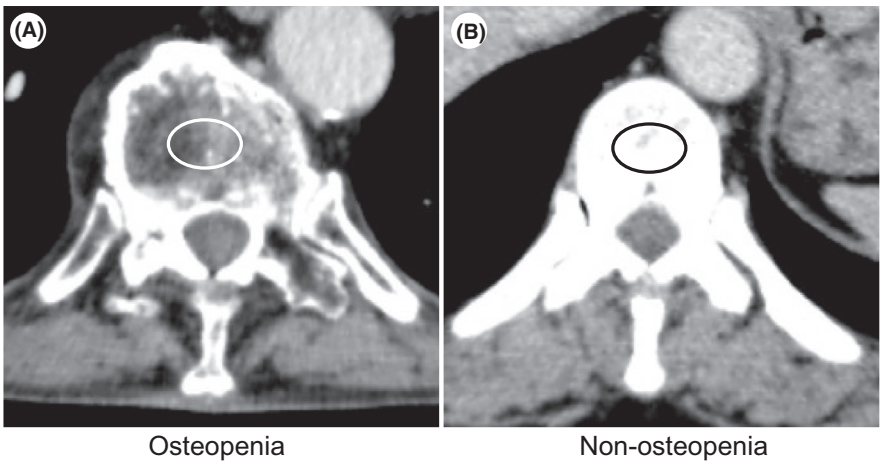

FIGURE 1 We calculated the average pixel density of the trabecular bone to analyze bone mineral density by placing elliptical regions of interest in the mid-vertebral core of the 11th thoracic vertebra on preoperative enhanced CT. A: Osteopenia and B: nonosteopenia. CT, computed tomography

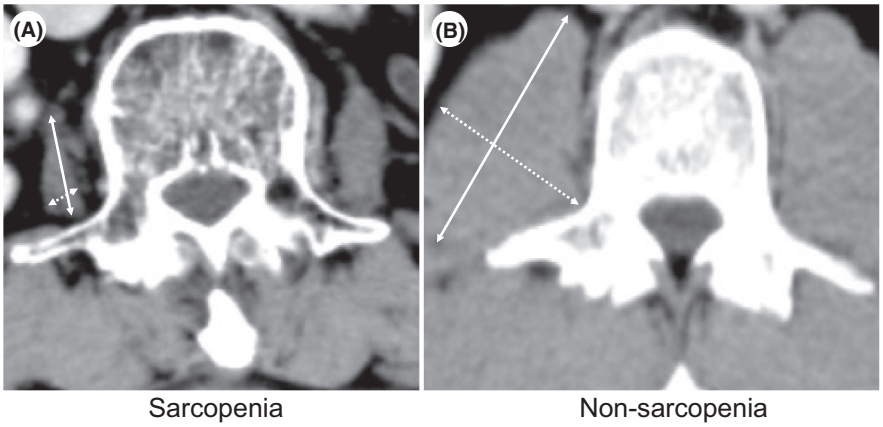

FIGURE 2 We calculated the psoas muscle mass area at the level of the third lumbar vertebra using the following formula: length of the major axes (continuous line) × the length of the minor axes (dotted line) × π. A, Sarcopenia, B, nonosteopenia

infection, ileus, and intraperitoneal abscess were observed in 10 (4.4%), 29 (12.6%), 18 (7.8%), and 13 patients (5.7%), respectively.

The median follow-up durations for DFS and OS were 61.4 (range: 1.2–118) and 65.6 (range: 1.2–118) mo, respectively. During the follow-up period, 49 patients (21.3%) developed recurrences and 45 (19.6%) died. Adjuvant chemotherapy was administered to 101 patients (43.9%), chemotherapy was performed in 24 (10.4%) patients with unresectable recurrence and metastatic tumors, and surgical resection was performed in 22 (9.56%) patients with resectable recurrence and metastatic tumors. The 5-y DFS and OS rates after laparoscopic colorectal resection for CRC were 77.9% and 82.5%, respectively.

In univariate analysis, osteopenia was significantly more common in older, female, and sarcopenia patients ($P = .02$, $P < .01$, $P < .01$, respectively); BMI and BMD were significantly lower in patients with osteopenia ($P = .01$, $P < .01$, respectively).

3.2 | Univariate and multivariate DFS analyses of patients with CRC

Table 2 shows the relation between the clinicopathological characteristics and the DFS rates after laparoscopic colorectal resection for CRC. In univariate analysis, the DFS rate was significantly worse in patients with stage II, III cancer ($P < .01$), vascular invasion ($P < .01$), carcinoembryonic antigen (CEA) levels > 5.0 ng/mL ($P < .01$), CA19-9 > 37.0 ($P < .01$), sarcopenia ($P < .01$), and osteopenia ($P < .01$). In multivariate analysis, stage II, III cancers (hazard ratio [HR]: 3.06; 95% confidence interval [CI]: 1.26–7.39; $P = .01$), vascular invasion (HR: 3.36; 95% CI: 1.27–8.85; $P = .01$), CEA > 5.0 ng/mL (HR: 2.69; 95% CI: 1.48–4.90; $P < .01$), and osteopenia (HR: 6.75; 95% CI: 3.62–12.6; $P < .01$) were significant independent predictors of DFS.

3.3 | Impact of osteopenia and sarcopenia on DFS after colorectal resection for CRC

Patients with osteopenia had significantly lower DFS rates than those without (5-y survival rates, 51.4% vs 83.7%; $P < .01$; Figure 3A). The Kaplan–Meier curve showed that the patients with osteopenia, regardless of sex, had worse DFS rates compared to those without osteopenia (log-rank $P < .01$ and $P < .01$; Figure 3B,C). Similarly, the patients with sarcopenia had significantly worse DFS rates than those without sarcopenia (5-y survival rates, 69.9% vs 85.9%; $P < .01$; Figure 5A).

3.4 | Univariate and multivariate OS analyses of patients with CRC

Table 3 shows the relation between the clinicopathological characteristics and the OS rate after laparoscopic colorectal resection for CRC. In the univariate analysis, the OS rate was significantly worse in patients with stage II, III cancer ($P = .03$), CEA > 5.0 ng/mL ($P < .01$), CA19-9 > 37.0 ($P < .01$), sarcopenia ($P < .01$), and osteopenia ($P < .01$). In the multivariate analysis, CEA > 5.0 (HR: 1.92; 95% CI: 1.04–3.52; $P = .04$), CA19-9 > 37.0 (HR: 2.05; 95% CI: 1.01–4.15; $P = .05$), and osteopenia (HR: 5.10; 95% CI: 2.72–9.57; $P < .01$) were significant independent predictors of OS.

3.5 | Impact of osteopenia and sarcopenia on OS after colorectal resection for CRC

OS was significantly lower in patients with than in those without osteopenia (5-y survival rates, 56.1% vs 88.4%; $P < .01$; Figure 4A). The Kaplan–Meier curve indicated that, irrespective of sex, the patients with osteopenia had a worse OS rate than those without (log-rank $P < .01$, $P < .01$; Figure 4B,C). Furthermore, during the follow-up period, 28 patients (12.2%) developed cancer-specific death, and the 5-y cancer-specific survival (CSS) rates after laparoscopic colorectal resection for CRC were 88.8%. The Kaplan–Meier curve indicated that patients with osteopenia had worse CSS rates than those without osteopenia (5-y survival rates, 72.2% vs 92.3%, log-rank $P < .01$; Figure 4D). Similarly, the OS rate was significantly lower in patients with than in those without sarcopenia (5-y survival rates, 75.8% vs 89.4%; $P < .01$; Figure 5B).

4 | DISCUSSION

Our results showed that osteopenia could be a long-term prognostic factor for DFS, OS, and CSS in patients with CRC. To our knowledge, this is the first report to demonstrate the impact of osteopenia on CRC mortality (regardless of sex) and to compare this risk factor with sarcopenia.

Recently, many studies have shown that sarcopenia and malnutrition are significantly associated with the quality of life and prognosis in patients with cancer.[2] Sarcopenia is defined as a complex syndrome, characterized by a progressive and generalized loss of both skeletal muscle mass and strength because of a series of chronic diseases and cancers. In previous reports, sarcopenia was shown to be a prognostic factor in CRC. Kroenke et al suggested that among 3262 patients with CRC, those with low skeletal muscle radiodensity and muscle mass (ie, sarcopenia) had the highest overall risk of disease-specific and overall mortality rates (HR: 2.02; 95% CI: 1.65–2.47) and CRC-specific mortality rates (HR: 2.54; 95% CI: 1.91–3.37).[2] Wang et al reported that the preoperative low L3 skeletal muscle index adversely affected the DFS (HR: 1.894; 95% CI: 1.330–2.698; $P < .001$) and OS (HR: 2.030; 95% CI: 1.420–2.902; $P < .001$) rates in 400 patients with CRC.[15] Furthermore, the GPS was considered an effective system for predicting CRC recurrence and patient prognosis. Lu et al performed a meta-analysis including 9839 patients with CRC, and stated that elevated or modified GPS was associated with poor OS rates (HR: 2.20, 95% CI: 1.88–2.57,

TABLE 1 Clinicopathological and surgical characteristics of 230 patients who underwent laparoscopic colorectal resection for colorectal cancers

Factors	Total	Osteopenia	Nonosteopenia	*P*-value
		n (%) or median (range)		
Patients	230	43	187	
Age (y)	67 (32–89)	71 (49–88)	66 (32–89)	.02
Sex				
Male	136 (59.2%)	17 (39.5%)	119 (63.6%)	<.01
Female	94 (40.8%)	26 (60.5%)	68 (36.4%)	
Body mass index (kg/m^2)	22.1 (13.9–43.5)	21.3 (13.9–32.1)	22.1 (14.6–43.5)	.01
Histopathology				.97
tub1	163 (70.8%)	29 (67.4%)	134 (71.7%)	
tub2	57 (24.8%)	12 (27.9%)	45 (24.1%)	
por	4 (1.7%)	1 (2.3%)	3 (1.6%)	
muc	4 (1.7%)	1 (2.3%)	3 (1.6%)	
pap	1 (0.5%)	0	1 (0.5%)	
Endocrine cell carcinoma	1 (0.5%)	0	1 (0.5%)	
Primary tumor location				.08
Cecum	12 (5.2%)	2 (4.7%)	10 (5.4%)	
Ascending colon	37 (16.1%)	12 (27.9%)	25 (13.4%)	
Transverse colon	19 (8.3%)	1 (2.3%)	18 (9.6%)	
Descending colon	7 (3.0%)	0	7 (3.7%)	
Sigmoid colon	54 (23.5%)	7 (16.3%)	47 (25.1%)	
Rectum	101(43.9%)	21 (48.8%)	80 (42.8%)	
Operative procedure				.42
Ileocecal resection	16 (6.9%)	4 (9.3%)	12 (6.3%)	
Right hemicolectomy	43 (18.7%)	11 (25.6%)	32 (17.1%)	
Transverse colectomy	2 (0.9%)	0	2 (1.1%)	
Left hemicolectomy	14 (6.1%)	0	14 (7.5%)	
Sigmoid colectomy	52 (22.6%)	7 (16.3%)	45 (24.1%)	
Rectal anterior resection	68 (29.6%)	13 (30.2%)	55 (29.4%)	
Abdominoperineal resection	32 (13.9%)	7 (16.3%)	25 (13.4%)	
Intersphincteric resection	3 (1.3%)	1 (2.3%)	2 (1.1%)	
Lymph node dissection				.34
D1	14 (6.1%)	3 (6.9%)	11 (5.9%)	
D2	76 (33.0%)	18 (41.9%)	58 (31.0%)	
D3	140 (60.9%)	22 (51.2%)	118 (63.1%)	
Pathological stage				.87
I	73 (31.7%)	15 (34.9%)	58 (31.1%)	
II	65 (28.3%)	12 (27.9%)	53 (28.3%)	
III	92 (40.0%)	16 (37.2%)	76 (40.6%)	
Adjuvant chemotherapy	101 (43.9%)	14 (32.6%)	87 (46.5%)	.10
Obstructive colorectal cancer	11 (4.8%)	2 (4.7%)	9 (4.8%)	.96
Operative time (min)	275 (115–513)	275 (123–485)	275 (115–513)	.61
Intraoperative blood loss (mL)	43 (5–970)	40 (5–970)	45 (5–900)	.91
Calcium levels (mg/dL)	9.3 (7.0–10.8)	9.2 (7.0–10.5)	9.3 (7.2–10.8)	.85

(Continues)

TABLE 1 (Continued)

Factors	Total	Osteopenia	Nonosteopenia	*P*-value
		n (%) or median (range)		
BMD (HU)	221.3	104.2	248.1	<.01
	(16.8–691.7)	(16.8–170.6)	(150.6–691.7)	
Sarcopenia	114 (49.6%)	32 (74.4%)	82 (43.9%)	<.01
Complications				
Anastomotic leakage	10 (4.4%)	4 (9.3%)	6 (3.2%)	.08
Surgical site infection	29 (12.6%)	5 (11.6%)	24 (12.8%)	.83
Ileus	18 (7.8%)	5 (11.6%)	13 (7.0%)	.30
Intraperitoneal abscess	13 (5.7%)	2 (4.7%)	11 (5.9%)	.75

Abbreviations: BMD, bone mineral density; muc, mucinous adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; tub1, well-differentiated tubular adenocarcinoma; tub2, moderately differentiated tubular adenocarcinoma.

$P < .001$) and worse cancer-specific survival rates (HR: 1.86, 95% CI: 1.59–2.17, $P < .001$).[16]

Osteopenia has recently been considered as sarcopenia interrelated with BMD loss; however, few reports have addressed the prognostic value of osteopenia in patients with CRC. BMD is a composite biomarker of exposure to various factors throughout a patient's lifetime and is positively associated with estrogens, calcium and vitamin D intake, weight, and physical activity that is combined with genetics and ethnicity. These factors play a crucial role in the development and maintenance of BMD.[17] BMD is related to the factors that negatively (aging, BMI, smoking, alcohol) or positively (calcium, vitamin D, oral contraceptives, physical activity) affect the CRC risk.[18]

To date, two studies have analyzed the association between CRC and BMD.[18,19] Ganry et al performed analyses of the data of 1471 women aged ~60 y, and reported that 31 cases of colon cancer were observed; the standardized incidence ratio decreased with increasing BMD, showing a significantly decreased risk (20%) in women with a higher BMD compared to those with a lower BMD.[18] Furthermore, Zhang et al used the data of 1394 women from Massachusetts, and reported that 44 colon cancer cases occurred; the rate ratios of colon cancer were 1.0, 0.7 (95% CI: 0.3–1.3), and 0.4 (95% CI: 0.2–0.9) from the lowest to the highest tertile of the bone mass ($P = .033$).[19]

We note that these two previous studies only reported significant associations between BMD and colon cancer in women. The relationship between the estrogen levels and BMD has been recognized for decades. Estrogen is known to play an important role in maintaining bone remodeling and balancing osteoblast and osteoclast activity[20]; additionally, women treated with hormone replacement therapy had a significantly higher BMD.[21] As previously reported, these results suggested that the skeletal status may serve as a proxy for cumulative estrogen exposure[19]; thus, high levels of such exposure could protect against the development of colon cancer.

Our results showed that sarcopenia and GPS were not significantly associated with the OS and DFS rates after performing multivariate analysis; however, osteopenia was significantly associated with the OS and DFS rates of patients with CRC, regardless of sex (DFS: male: $P < .01$, female: $P < .01$; OS: male: $P < .01$, female: $P < .01$). To our knowledge, no prior studies have reported the long-term prognostic association between osteopenia and CRC; thus, these results are valuable. Although several studies have shown that higher dietary intake of calcium and circulating levels of vitamin D metabolites are associated with lower CRC incidence and mortality,[22,23] the biological mechanisms linking BMD to the prognosis of CRC remain unclear. However, high calcium levels have been shown to induce higher levels of apoptosis in the colon epithelium, thereby exhibiting an antineoplastic effect.[24,25] Additionally, vitamin D may act directly on the colon epithelium; thus, helping to maintain calcium homeostasis by regulating apoptosis and cellular differentiation, and by modulating the growth factor and cytokine levels.[26] Furthermore, as the synthesizing enzyme of vitamin D, elevated CYP27B1 levels suggested a possible benefit of vitamin D treatment, especially in well and moderately differentiated adenocarcinoma; conversely, a relatively low expression of CYP27B1 in poorly differentiated adenocarcinoma indicated resistance of the cancer cells to vitamin D action.[27]

In this study, we analyzed the BMD by calculating the average pixel density of the trabecular bone in the mid-vertebral core of the 11th thoracic vertebra on preoperative enhanced CT. Dual-energy x-ray absorptiometry (DEXA) of the hips and the lumbar spine is a widely recognized diagnosis tool for osteoporosis in the orthopedics area. However, in digestive surgery area, DEXA remains an uncommon tool, and requires an additional cost, patient time, equipment, or radiation exposure. Pickhardt et al[28] performed CT for BMD assessment instead of DEXA and reported that a threshold of ≤160 HU, according to the CT-derived assessment, presented 90% sensitivity; in contrast, after setting the threshold to ≥110 HU, they observed a >90% specificity for differentiating osteoporosis from osteopenia and normal BMD. Unfortunately, preoperative assessment of nutritional factors, such as calcium or vitamin D levels and estrogen intake using food frequency self-questionnaires, or snapshots of serum biomarkers, may be susceptible to measurement bias[18]; furthermore, these factors have been shown to modify the levels of cell differentiation and apoptosis in the colon epithelium.[24,25] In fact, our

TABLE 2 Clinicopathological factors in relation to the DFS rates after laparoscopic colorectal resection for colorectal cancers by univariate and multivariate analyses

		DFS univariate analysis		DFS multivariate analysis	
Factors	**n**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Male					
Yes	136	1.11	.72		
No	94	(0.62–1.97)			
Right-sided colon cancer					
Yes	68	0.84	.59		
No	162	(0.45–1.59)			
Obstructive colorectal cancer					
Yes	11	1.89	.22		
No	219	(0.68–5.29)			
GPS					
Yes	12	1.10	.89		
No	239	(0.27–4.53)			
GPS					
1 or 2	35	0.62	.31		
0	195	(0.24–1.56)			
Stage					
II, III	157	3.86	<.01	3.06	.01
I	73	(1.65–9.09)		(1.26-7.39)	
Vascular invasion					
Yes	165	3.96	<.01	3.36	.01
No	65	(1.57–10.0)		(1.27-8.85)	
CEA > 5.0					
Yes	68	3.36	<.01	2.69	<.01
No	162	(1.91–5.91)		(1.48-4.90)	
CA19-9 > 37.0					
Yes	28	3.00	<.01	1.96	.05
No	202	(1.56–5.76)		(0.99-3.88)	
Osteopenia					
Yes	43	4.45	<.01	6.75	<.01
No	187	(2.51–7.89)		(3.62-12.6)	
Sarcopenia					
Yes	114	2.58	<.01	1.79	.07
No	116	(1.40–4.74)		(0.96-3.34)	
Anastomotic leakage					
Yes	10	1.77	.34		
No	220	(0.55–5.68)			
Surgical site infection					
Yes	29	1.67	.16		
No	201	(0.81–3.43)			
Ileus					
Yes	18	1.55	.35		
No	212	(0.62–3.91)			

(Continues)

TABLE 2 (Continued)

Factors	n	DFS univariate analysis		DFS multivariate analysis	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Intraperitoneal abscess					
Yes	13	2.22	.09		
No	217	(0.88–5.59)			
All complications					
Yes	56	1.66	.10		
No	174	(0.92–3.02)			

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; GPS, Glasgow Prognostic Score.

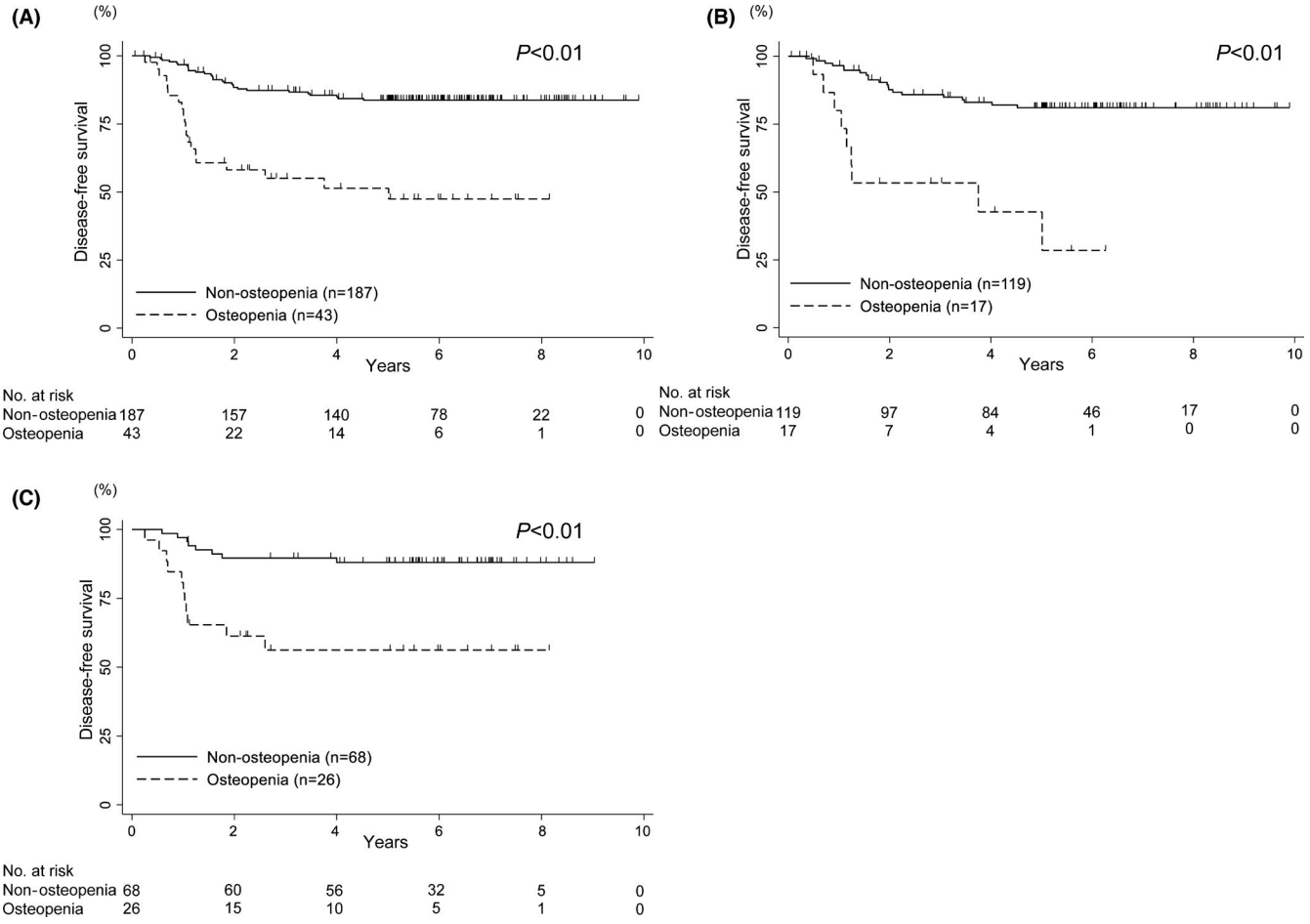

FIGURE 3 Kaplan–Meier curves, separated by sex, are shown for disease-free survival after operation for colorectal cancer in patients with and in those without osteopenia. A: All patients, B: men, and C: women

results showed that the serum calcium levels were not associated with osteopenia. Furthermore, measuring the serum vitamin D or estrogen levels needs time and effort and, therefore, these levels are not commonly assessed in patients with CRC. Utilizing BMD by CT as an objective marker for cumulative exposure to these multiple factors may be a useful, simple, and minimally invasive method in patients with CRC.

In addition, in this study osteopenia was associated with significantly lower DFS and OS rates ($P < .01$, $P < .01$, respectively); nevertheless, such associations were not observed in sarcopenia cases ($P = .07$, $P = .33$, respectively). Numerous studies have supported the concept of a bone-muscle unit, where there is constant crosstalk between the two tissues. In 2015, Tagliaferri et al provided an in-depth analysis, including studies that considered bone as the target of skeletal muscle secretory pattern or others that described the potential effects of bone on muscle metabolism.[29] In their analysis, the authors described the potential roles of cartilage, tendon, and adipose tissue in the musculoskeletal control loop. They first

TABLE 3 Clinicopathological factors in relation to the OS rates after laparoscopic colorectal resection for colorectal cancers by univariate and multivariate analyses

		OS univariate analysis		OS multivariate analysis	
Factors	**n**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Male					
Yes	136	1.34	.34		
No	94	(0.72–2.47)			
Right-sided colon cancer					
Yes	68	1.47	.21		
No	162	(0.81–2.69)			
Obstructive colorectal cancer					
Yes	11	2.46	.09		
No	219	(0.88–6.89)			
GPS					
Yes	12	1.10	.89		
No	239	(0.27–4.53)			
GPS					
1 or 2	35	1.37	.41		
0	195	(0.64–2.96)			
Stage					
II, III	157	2.38	.03	2.12	.06
I	73	(1.11–5.10)		(0.97–4.65)	
Vascular invasion					
Yes	165	2.13	.05		
No	65	(0.99–4.56)			
CEA > 5.0					
Yes	68	2.34	<.01	1.92	.04
No	162	(1.30–4.21)		(1.04–3.52)	
CA19-9 > 37.0					
Yes	28	2.84	<.01	2.05	.05
No	202	(1.44–5.63)		(1.01–4.15)	
Osteopenia					
Yes	43	5.13	<.01	5.10	<.01
No	187	(2.84–9.27)		(2.72–9.57)	
Sarcopenia					
Yes	114	2.51	<.01	1.41	.33
No	116	(1.33–4.72)		(0.71–2.79)	
Anastomotic leakage					
Yes	10	2.45	.09		
No	220	(0.87–6.84)			
Surgical site infection					
Yes	29	1.32	.49		
No	201	(0.59–2.96)			
Ileus					
Yes	18	2.15	.08		
No	212	(0.91–5.08)			

(Continues)

TABLE 3 (Continued)

Factors	n	OS univariate analysis		OS multivariate analysis	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Intraperitoneal abscess					
Yes	13	1.46	.53		
No	217	(0.45–4.71)			
All complications					
Yes	56	1.57	.16		
No	174	(0.83–2.95)			

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; GPS, Glasgow Prognostic Score; OS, overall survival.

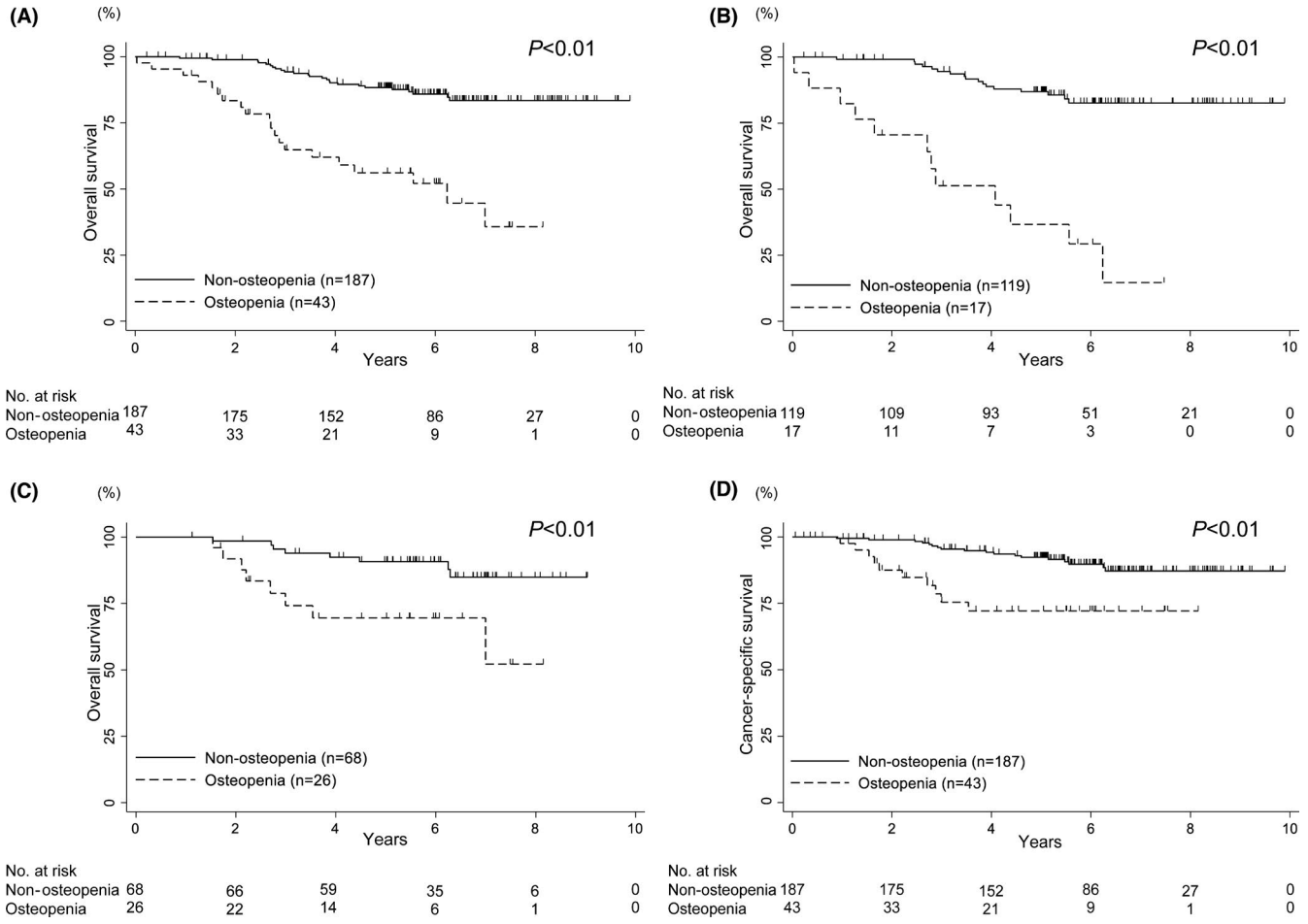

FIGURE 4 Kaplan–Meier curves, separated by sex, are presented for overall survival after operation for colorectal cancer between patients with and those without osteopenia. A: All patients, B: men, and C: women. D: Kaplan–Meier curves are presented for cancer-specific survival after operation for colorectal cancer in patients with and in those without osteopenia

reviewed the concept of the "bone-muscle unit," phenotypically evidenced by the observation of a linear relationship between bone mineral content or density and lean body mass at various ages. Our results supported this concept of a bone-muscle unit. Thus, osteopenia was considered a result of the progression of sarcopenia; in fact, most patients with osteopenia in our cohort had sarcopenia (32/43 patients; 74.4%). Furthermore, interestingly, osteopenia might be a risk factor of survival for not only CRC patients, but also the general population. It can be seen from Figure 4 that the late phase of the survival curve was not changed in CSS, but continued to decrease in OS.

BMD can be expected to improve with preoperative treatment. Adequate nutrition (such as calcium and vitamin D intake), exercise, and the hormonal environment could play an important role in preventing osteopenia. Furthermore, antiresorptive drugs, including estrogen, selective estrogen receptor modulators, and

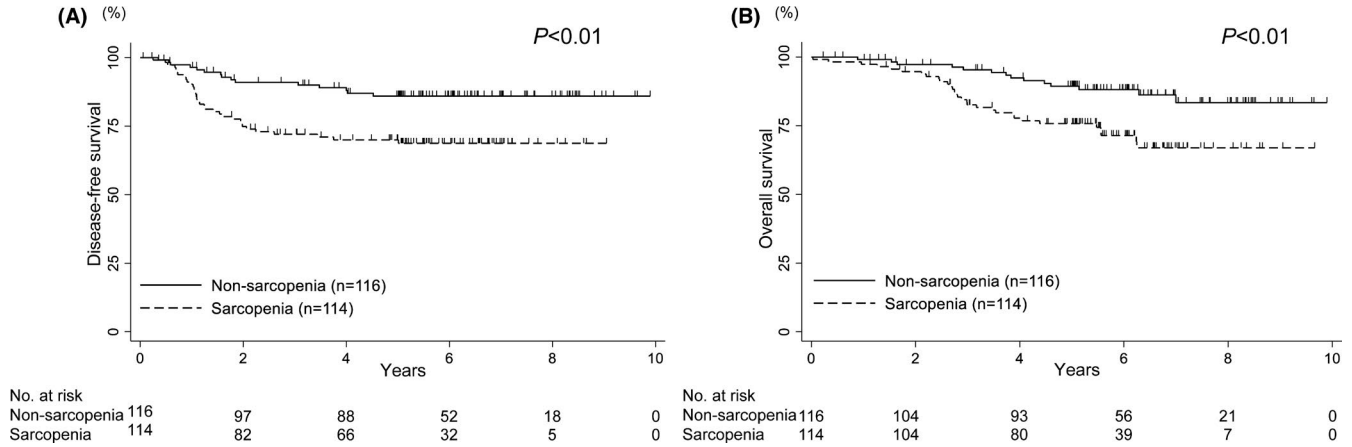

FIGURE 5 A: Kaplan–Meier curves are presented for disease-free survival after operation for colorectal cancer in patients with and in those without sarcopenia. B: Kaplan–Meier curves are presented for overall survival after operation for colorectal cancer in patients with and in those without sarcopenia

bisphosphonates or anabolic agents to stimulate bone formation, including parathyroid hormone, could offer benefits for patients with osteopenia. Early interventions, such as any or a combination of these therapies, might improve the outcomes of not only CRC patients with osteopenia but also general people with osteopenia.[30]

Our study had several limitations. The most important limitation was the fact that this retrospective study was conducted at a single institution with a small number of cases. Moreover, the confounding effects of the existing risk factors for CRC cannot be ruled out. The definitions of sarcopenia and osteopenia are controversial, and racial differences are also possible. Thus, studies using data from large-scale multicenter registries or prospective studies are necessary to be conducted in the future.

5 | CONCLUSION

This retrospective study showed that preoperative osteopenia was significantly associated with worse DFS and OS rates in patients who underwent resection for CRC. The measurement of BMD by enhanced CT might be a useful tactic for diagnosing osteopenia and a prognostic indicator that can be used in patients with CRC.

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None.

DISCLOSURE

Conflict of interest: The authors declare no conflicts of interest for this article.

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the International University of Health and Welfare Hospital (approval no: 20-B-451). All data were subject to strict privacy policies, and the patients or their family members had the option to drop out of the study at any time. The requirement for acquisition of informed consent from patients was waived because of the retrospective design of this study and anonymized data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Kroenke CH, Prado CM, Meyerhardt JA, et al. Muscle radiodensity and mortality in patients with colorectal cancer. Cancer. 2018;124(14):3008–15.
3. Miyamoto Y, Baba Y, Sakamoto Y, et al. Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. Ann Surg Oncol. 2015;22(8):2663–8.
4. Looijaard SMLM, Te Lintel Hekkert ML, Wüst RCI, Otten RHJ, Meskers CGM, Maier AB. Pathophysiological mechanisms explaining poor clinical outcome of older cancer patients with low skeletal muscle mass. Acta Physiol. 2021;231(1):e13516.
5. Blain H, Jaussent A, Thomas E, et al. Appendicular skeletal muscle mass is the strongest independent factor associated with femoral neck bone mineral density in adult and older men. Exp Gerontol. 2010;45(9):679–84.
6. Urashima M, Ohdaira H, Akutsu T, et al. Effect of vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial. JAMA. 2019;321(14):1361–9.
7. Yang W, Giovannucci EL, Hankinson SE, et al. Endogenous sex hormones and colorectal cancer survival among men and women. Int J Cancer. 2020;147(4):920–30.

8. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42.
9. Japanese Society for Cancer of the Colon and Rectum. Japanese classification of colorectal, appendiceal, and anal carcinoma: the 3d English edition. J Anus Rectum Colon. 2019;3(4):175–95.
10. Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. Ann Oncol. 2018;29(7):1528–34.
11. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003;89(6):1028–30.
12. Toshima T, Yoshizumi T, Ikegami T, et al. Impact of osteopenia in liver cirrhosis: special reference to standard bone mineral density with age. Anticancer Res. 2018;38(11):6465–71.
13. Sharma P, Parikh ND, Yu J, et al. Bone mineral density predicts post-transplant survival among hepatocellular carcinoma liver transplant recipients. Liver Transpl. 2016;22(8):1092–8.
14. Masuda T, Shirabe K, Ikegami T, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl. 2014;20(4):401–7.
15. Wang S, Xie H, Gong Y, et al. The value of L3 skeletal muscle index in evaluating preoperative nutritional risk and long-term prognosis in colorectal cancer patients. Sci Rep. 2020;10(1):8153.
16. Xin L, Wanying G, Wei X, et al. Prognostic value of the Glasgow prognostic score in colorectal cancer: a meta-analysis of 9,839 patients. Cancer Manag Res. 2018;11:229–49.
17. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. Am J Clin Nutr. 2002;75(4):773–9.
18. Ganry O, Lapôtre-Ledoux B, Fardellone P, Dubreuil A. Bone mass density, subsequent risk of colon cancer and survival in postmenopausal women. Eur J Epidemiol. 2008;23(7):467–73.
19. Zhang Y, Felson DT, Ellison RC, et al. Bone mass and the risk of colon cancer among postmenopausal women: the Framingham study. Am J Epidemiol. 2001;153(1):31–7.
20. Parfitt AM. Quantum concept of bone remodelling and turnover: implications for the pathogenesis of osteoporosis. Calcif Tissue Int. 1979;28(1):1–5.
21. Maddalozzo GF, Widrick JJ, Cardinal BJ, Winters-Stone KM, Hoffman MA, Snow CM. The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. Bone. 2007;40(5):1244–51.
22. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer. 2009;61(1):47–69.
23. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Ailment Pharmacol Ther. 2009;30(2):113–25.
24. Penman ID, Liang QL, Bode J, Eastwood MA, Arends MJ. Dietary calcium supplementation increases apoptosis in the distal murine colonic epithelium. J Clin Pathol. 2000;53(4):302–7.
25. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. Cancer Prev Res (Phila). 2009;2(3):213–23.
26. Harris DM, Go VLW. Vitamin D and colon carcinogenesis. J Nutr. 2004;134(12 Suppl):3463S–71S.
27. Dou R, Ng K, Giovannucci EL, Manson JE, Qian ZR, Ogino S. Vitamin D and colorectal cancer: molecular, epidemiological and clinical evidence. Br J Nutr. 2016;115(9):1643–60.
28. Pickhardt PJ, Pooler BD, Lauder T, et al. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. Ann Intern Med. 2013;158:588–95.
29. Tagliaferri C, Wittrant Y, Davicco MJ, Walrand S, Coxam V. Muscle and bone, two interconnected tissues. Ageing Res Rev. 2015;21:55–70.
30. Chen LR, Ko NY, Chen KH. Medical treatment for osteoporosis: from molecular to clinical opinions. Int J Mol Sci. 2019;20(9):2213.

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