RESEARCH ARTICLE

Serum 25-hydroxy Vitamin D Status is Not Related to Osteopenia/Osteoporosis Risk in Colorectal Cancer Survivors

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Abstract

Background: The incidence of colorectal cancer increases with vitamin D deficiency as shown in recently published studies. In addition, prospective investigations have indicated that low vitamin D levels may be associated with increased mortality of colorectal cancer, especially in stage III and IV cases. However, the exact incidence of vitamin D deficiency and the relation between vitamin D deficiency and osteopenia/osteporosis is still not known. The aim of this study is to identify severity of vitamin D deficiency and absolute risk factors of osteopenia/osteoporosis in colorectal cancer survivors. Materials and Methods: A total of 113 colorectal cancer survivors treated with surgery and/or chemotherapy ± radiotherapy were recruited from medical oncology outpatient clinics during routine follow-up visits in 2012-2013. Bone mineral densitometry (BMD) was performed, and serum 25-OH vitamin D levels were also checked on the same day of the questionnaire. The patients was divided into 2 groups, group A with normal BMD and group B with osteopenia/osteoporosis. Results: The median age of the study population was 58 (40-76). Thirty (30.0%) were female, whereas 79 (70.0%) were male. The median follow-up was 48 months (14-120 months). Vitamin D deficiency was found in 109 (96.5%); mild deficiency (20-30 ng/ml) in 19 (16.8%), moderate deficiency (10-20 ng/ml) in 54 (47.8%) and severe deficiency (<10 ng/ml) in 36 (31.9%). Osteopenia was evident in 58 (51.4%) patients whereas osteoporosis was noted in 17 (15.0%) . Normal BMD was observed in 38 (33.6%). No apparent effects of type of surgery, presence of stoma, chemotherapy, radiotherapy and TNM stage were found regarding the risk of osteopenia and osteoporosis. Also, the severity of the vitamin D deficiency had no effect in the risk of osteopenia and osteporosis (p=0.93). In female patients, osteopenia/osteoporosis were observed in 79.5% patients as compared to 60.7% of male patients (p=0.04). Conclusions: In our study, vitamin D deficiency and osteopenia/osteoporosis was observed in 96.5% and 66.4% of colorectal cancer survivors, respectively. There is no defined absolute risk factor of osteopenia and osteoporosis in colorectal cancer survivors. To our knowledge, in the literature, our study is the first to evaluateall the risk factors of osteopenia and osteoporosis in colorectal cancer survivors.

Keywords: Colorectal cancer - cancer - vitamin D - osteopenia - osteoporosis

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Introduction

Colorectal cancer is still the third most frequently diagnosed and third leading cancer death in both sexes in the United States despite the incidence and death rates have decreased over the past two decades (Siegel et al., 2011; 2013). With earlier diagnosis though screening modalities and new better treatment alternatives, colorectal cancer is being transformed from incurable disease to an illness that is increasingly curable. As a result of improvements in the treatment of colorectal cancer, the importance of the long-term follow-up has brought more attention to and led to increased interest in the unique problems, risks, needs, and concerns of survivors who have completed treatment.

Preclinical and epidemiological studies indicates that both active metabolite of vitamin D and analogues of vitamin D may have potential as anticancer agents because their administration has antiproliferative effects and vitamin D can activate apoptotic pathways and inhibit angiogenesis (Deeb et al., 2007; Trump et al., 2010). In addition, vitamin D can potentiate the anticancer effects of many cytotoxic and antiproliferative anticancer agents which was shown in vivo and in vitro studies (Moffatt et al., 1999; Hershberger et al., 2001; Ma et al., 2008). Observational studies have revealed possible relation between vitamin D deficiency and the risk of many cancers (Holick, 2007). Both prospective and retrospective

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epidemiologic studies demonstrated that risk of colorectal cancer, prostate cancer and breast cancer increased by 30 to 50 percent in vitamin D deficient people (Feskanich et al., 2004; Gorham et al., 2005; Garland et al., 2006; Giovannucci et al., 2006). And also the risk of Hodgkin Lymphoma, pancreatic cancer and ovarian cancer have increased in vitamin D deficient people (Holick, 2007).

Colorectal cancer was identified as the type of cancer with the greatest risk associated with vitamin D deficiency by World Health Organization (WHO). In the combined analysis of Nurses' Health Study (NHS) cohort study and case–control Health Professionals Follow-up Study (HPFS), higher plasma 25-hydroxy vitamin D levels associated with significantly decreased risk of colorectal cancer compared to lower levels of plasma 25-hydroxy vitamin D levels (Wu et al., 2007). An observational cohort study showed inverse association between levels of pre-diagnostic 25-hydroxy vitamin D concentration and risk of colorectal cancer in European populations in European populations (Jenab et al., 2010). In a meta-analyses of prospective studies 1.822 colon and 868 rectal cancers were included; significant inverse association between risk of colorectal cancer and serum 25-hydroxy vitamin D levels was found. (Lee et al., 2011). Another meta-analysis of nine case-control studies, showed that each 4 ng/mL (10 nmol/L) increase in pre-diagnosis serum 25-hydroxy vitamin concentration was associated with a 6 percent decrease in colorectal cancer prevalence (Chung et al., 2011). In a meta-analysis of 9 prospective studies 2.767 cases and 3.948 controls (total 6466) were included; the results indicated that lower 25-hydroxy vitamin D levels were inversely associated with colorectal cancer risk and 10 ng/ml increment of 25-hydroxy vitamin D levels associated with a relative risk of 0.74 (95%CI, 063-0.95) (Ma et al., 2011).

A meta-analysis of 5 prospective study have demonstrated that higher plasma 25-hydroxy vitamin D levels associated with 51% decrease of colorectal cancer risk (Gorham et al., 2007). In the follow up of 304 colorectal cancer patients in NHS and HPFS trials, higher pre-diagnosis plasma 25-hydroxy vitamin D levels were associated with significant improvement in overall survival (OS) (Ng et al., 2008). In the follow up of 1.017 colorectal cancer patients in NHS and HPFS trials, higher post-diagnosis plasma 25-hydroxy vitamin D levels were associated with significant reduction of colorectal cancer-specific mortality and OS (Ng et al., 2009). In an Intergroup Trial N9741 study, prospectively 25-hydroxy vitamin D levels were measured in 515 stage IV colorectal cancer patients; 50% of the study population was vitamin D deficient and 82% were vitamin D insufficient (Ng et al., 2011). But in this study, no correlation was found between plasma 25-hydroxy vitamin D levels and patient outcomes in stage IV colorectal cancer.

Until now, no study has yet examined the whether vitamin D supplementation improves patient outcomes. Thus, It is not clear if these observed associations are causal as the current interventional data on the protective effect of vitamin D supplementation on the development of colorectal neoplasia are conflicting and additional studies are needed. In addition, the severity of vitamin D deficiency was not known in colorectal cancer survivors. Furthermore, the absolute risk factors of osteopenia/osteoporosis and vitamin D deficiency have not been defined in colorectal cancer survivors.+ The aim of this research is to identify severity of vitamin D deficiency and absolute risk factors of osteopenia/osteoporosis in colorectal cancer survivors. Thus, we prospectively investigated the severity of vitamin D deficiency and which treatment factors contributed to the development of osteopenia/osteoporosis in colorectal cancer survivors.

Materials and Methods

A total of 113 consecutive colorectal cancer survivors treated with surgery and/or chemotherapy±RT were recruited from medical oncology outpatient clinics during routine follow-up visits in 2012-2013. Patients younger than 40 years, bone metastatic patients, patients using biphosphonates and patients with osteopenia/osteoporosis history before diagnosis were excluded. Study patients had to be disease-free and off-treatment for at least 6 months at the time of evaluation. Medical information of patients was obtained from their medical records. Patients completed a survey questionnaire that was designed to obtain information about consisted of demographic characteristics and risk factors for osteopenia/osteoporosis. Bone mineral densitometry (BMD) was performed and serum 25-OH vitamin D levels were also checked on the same day of the questionnaire. Patients with vitamin D levels >30 ng/ml were categorized as sufficient, vitamin D levels between 20-30 ng/ml were categorized as mild deficiency, vitamin D levels between 10-20 ng/ml were categorized as moderate deficiency and vitamin D levels <10 ng/ml were categorized as severe deficiency. According to the BMD, T-score that is 2.5 standard deviations (SD) or more below the young-adult mean BMD is defined as osteoporosis whereas a T-score that is 1 to 2.5 SD below the young-adult mean is termed as osteopenia. Normal bone density is defined as a value within one standard deviation of the mean value in the young adult reference population (Kanis, 1994). The patients was divided into 2 groups according to the BMD scores. Group A is patients with normal BMD, whereas group B is patients with osteopenia/osteoporosis. Fracture Risk Assessment Tool (FRAX) score, which estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) for untreated patients between ages 40 and 90 years, was calculated for all study patients by using easily obtainable clinical risk factors for fracture and femoral neck BMD (g/cm^2) (Kanis et al., 2008).

In terms of the type of surgery; APR was performed in 13 (11.5%) patients, LAR was performed in 45 (39.8%) patients and colon surgery (left or right hemicolectectomy, sigmoid resection and transvers colectomy) was performed in 55 (48.7%) patients. Surgery was performed with different surgeons. Fourty rectal cancer (35.4%) patients were treated with postoperative chemoradiotherapy (with daily fluorouracil infusion). The total dose of radiotherapy (RT) was between 40-50Gy. No preoperative RT was performed.

We analyzed the impact of age, type of surgery, location of tumor, steroid usage, familial pathological fracture history, smoking status, chemotherapy, RT and the stage of the disease on the risk of osteopenia/osteoporosis.

Statistical analysis

All statistical analyses were performed by using SPSS for Windows version 18.0.(SPSS, Chicago, IL) Univariate statistical analyses were conducted to describe the demographic characteristics and medical treatment history of the patients in the study. Descriptive statistics, including frequencies, means, medians, and Standard deviations (SD), were calculated where appropriate. Student's t test, Mann–Whitney U test, and chi-square analyses were conducted as appropriate to compare patients with osteopenia/osteoporosis and patients with normal BMD. Two-sided p values of <0.05 were considered statistically significant.

Results

A total of 113 colorectal cancer survivors were included in this study. The median age of the study population was 58 (40-76). The median age was 56 (range, 41-81) and 62 (range, 43-83) in Group A and B, respectively (p=0.07). Thirty-four (30.0%) patients of the study population were female, whereas 79 (70.0%) patients were male. Rate of female patients was significantly higher in Group B compared to Group A (38.0% vs 18.4%, p=0.04). The median follow-up of the study population was 48 months (14-120 months). The mean interval between the end of active treatment and study evaluation was 32 months (8-114 months). Fifty-nine (52.2%) patients had colon cancer and 54 (47.8%) patients had rectal cancer. Fifteen (13.3%) patients had stage I disease, while 62 (54.9%), 28 (24.8%), and 8 (7.0%) patients had stage II, III and IV disease, respectively. All stage IV patients were tumor-free at the time of intervention (7 patients liver, 1 patient lung and liver metastasectomy). Only 87.6% of patients were treated with chemotherapy whereas 35.4% of patients were treated with RT. The median number of chemotherapy cycles was 6 (4-12) for both colon and rectal cancer.

The mean plasma 25-hydroxy vitamin D levels were 15.0±9.2 ng/ml in all the population. According to the plasma 25-hydroxy vitamin D levels, vitamin D deficiency was found in 109 (96.5%) of patients; mild deficiency in 19 (16.8%) patients, moderate deficiency in 54 (47.8%) patients and severe deficiency in 36 (31.9%) patients (Figure 1). Only 4 (3.5%) colorectal cancer survivors had sufficient plasma 25-hydroxy vitamin D levels. Osteopenia was found in 58 (51.4%) patients whereas osteoporosis was found in 17 (15.0%) patients. Normal BMD was found only in 38 (33.6%) of patients (Figure 2).

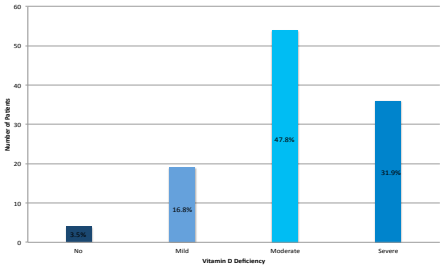

Figure 1. Severity of Vitamin D Deficiency in Colorectal Cancer Survivors

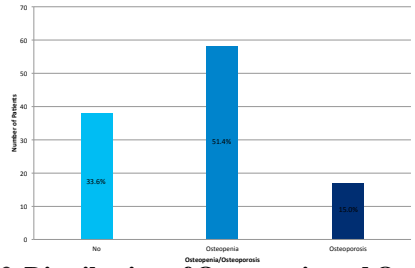

Figure 2. Distribution of Osteopenia and Osteoporosis in Colorectal Cancer Survivors

Table 1. Risk Factors of Osteopenia/Osteoporosis in Colorectal Cancer Survivors

Characteristic		Osteopenia/Osteoporosis No (n=38) n (%)		Yes (n=75) n (%)		p value*
Age	≤50	13	34.2	16	21.3	0.07
	51-64	18	47.4	30	40	
	≥65	7	18.4	29	38.7	
Body mass index	<25 kg/m^2	9	23.7	14	18.7	0.62
	≥25 kg/m^2	29	76.3	61	81.3	
Sex	Female	7	18.4	27	36	0.04
	Male	31	81.6	48	64	
Smoking History	No	12	31.6	38	50.7	0.1
	Exsmoker	9	23.7	9	12	
	Yes	17	44.7	28	37.3	
Pathological fracture history						
	No	37	97.4	75	100	0.33
	Yes	1	2.6	0	0	
Steroid usage	No	38	100	72	96	0.55
	Yes	0	0	3	4	
Location of tumor	Colon	21	55.3	38	50.7	0.89
	Rectum	17	44.7	37	49.3	
T-Stage at diagnosis	T1	0	0	1	1.3	0.85
	T2	5	13.2	12	16	
	T3	31	81.6	59	78.7	
	T4	2	5.2	3	4	
Lymph node status	N0	27	71.1	50	66.7	0.41
	N (+)	11	28.9	25	33.3	
TNM	Stage I	4	10.5	11	14.7	0.81
	Stage II	23	60.5	39	51	
	Stage III	9	23.7	19	25.3	
	Stage IV	2	5.3	6	8	
Type of surgery	APR	3	7.9	10	13.3	0.62
	LAR	14	36.8	29	38.7	
	Other**	21	55.3	36	48	
Presence of stoma	No	33	86.8	66	88	0.76
	Yes	5	13.2	9	12	
Chemotherapy	No	12	31.6	20	26.7	0.66
	Yes	26	68.4	55	74.3	
Radiotherapy	No	24	63.2	49	65.3	0.83
	Yes	14	36.8	26	34.7	
Vitamin D deficiency	No	1	2.6	3	4	0.93
	Mild	7	18.4	12	16	
	Moderate	17	44.7	37	49.3	
	Severe	13	34.2	23	30.7	

*p values of <0.05 were considered statistically significant; **Other; left hemicolectomy, right hemicolectomy, transvers colectomy and sigmoidectomy; Abbreviations: TNM, tumor-node-metastases; APR, abdomino-perineal resection; LAR, lower anterior resection

No apparent effect of type of surgery, presence of stoma, chemotherapy, radiotherapy and TNM stage was found in the risk of osteopenia and osteoporosis. Also, the severity of the vitamin D deficiency was no effect in the risk of osteopenia and osteporosis (p=0.93). In female patients, osteopenia/osteoporosis were observed in 79.5% patients whereas 60.7% of male patients (p=0.04). All of the risk factors of osteopenia/osteoporosis in colorectal cancer survivors are described in Table 1. According to the FRAX score, risk of ten year major osteoporotic fracture is 3.4% in colorectal cancer survivors.

Discussion

In our study, we examined the effect of severity of vitamin D deficiency, demographic and clinical risk factors on osteopenia and osteoporosis in colorectal cancer survivors. Vitamin D deficiency was found in 96.5% of colorectal cancer survivors and moderate-severe vitamin D deficiency was found in 79.7% of patients. Vitamin D levels were sufficient only in 3.5% of colorectal cancer survivors. In our study, osteopenia and osteoporosis was found in 66.4% of patients. In our study, no apparent effect of type of surgery, presence of stoma, chemotherapy, radiotherapy, TNM stage and severity of vitamin D deficiency in the risk of osteopenia and osteoporosis. Our study results show that female sex and increasing age cause higher risk of osteopenia and osteoporosis in colorectal cancer survivors. To our knowledge, in the literature, our study is the first study that evaluates all the risk factors of osteopenia and osteoporosis in colorectal cancer survivors.

Four meta-analyses of prospective studies reported significant inverse association between risk of colorectal cancer and serum 25-hydroxy vitamin D levels (Gorham et al., 2007; Chung et al., 2011; Lee et al., 2011; Ma et al., 2011). In a prospective study it was reported that higher pre-diagnosis plasma 25-hydroxy vitamin D levels were associated with significant improvement in OS (Ng et al., 2008). But no prospective study have investigated the prevalance of vitamin D deficiency in colorectal cancer survivors. In a retrospective study, vitamin D deficiency was found in 80.0% of patients with colorectal cancer, 15.0% were severely deficient (Maddipatla et al., 2007). In this retrospective study, the odds of being moderately or severe vitamin D deficiency was found to be 2.18 times higher in the group receiving chemotherapy as compared to patients who were not treated with chemotherapy. No statistical association of age, gender, stage and race were found with vitamin D deficiency (Maddipatla et al., 2007). In another study, patients receiving chemotherapy were 3.7 fold and patients with a rectal primary were 2.6-fold more likely to have severe vitamin D deficiency on multivariate analysis than non-chemotherapy patients and colon cancer primary patients, respectively (Fakih et al., 2009). In this study, no statistical association of age, sex, stage and body mass index were found with vitamin D deficiency (Fakih et al., 2009). Compared to this 2 study, in our study, we showed that vitamin D deficiency was found in 96.5% of colorectal cancer survivors; 31.9% of them is severe vitamin D deficiency. Due to the very high prevalence of vitamin D deficiency in our study population, no absolute risk factors could be defined.

It is well known that serum 25-hydroxy vitamin D levels were directly related with BMD especially when serum levels reached 40 ng/ml or more (Bischoff-Ferrari et al., 2006). In several of aromatase inhibitor studies in the adjuvant setting of breast cancer, aromatase inhibitors significantly increase bone loss and increase risk of pathological fracture compared to placebo or tamoxifen (Lonning et al., 2005; Perez et al., 2006; Eastell et al., 2008). In a large population retrospective study, risk of osteopenia and osteoporosis increased with anti-cancer treatment in patients with non-metastatic breast cancer (Boyce et al., 2005). In our study, due to the very high prevalence of vitamin D deficiency we could not show any correlation between vitamin D deficiency and the risk of osteopenia and osteoporosis.

Our study includes some limitations because of the cross sectional study. First, we have no healthy age-matched control group. Thus, misclassification bias can be possible. Second, the small number of the study population is another limitation of our study. Third, lifestyle changes and physical activity was not reported in our study. Another potential limitation of our study is that BMD and plasma 25-hyroxy vitamin D levels were only measured at the remission period in colorectal cancer periods who had to be disease-free and off-treatment for at least 6 months at the time of evaluation. Thus the baseline BMD and plasma 25-hyroxy vitamin D levels and the changes in time with treatment could not be assessed in our study. Also, we can not rule out the possibility of laboratory measurement errors.

In conclusion, we found a high prevalence of vitamin D deficiency (96.5%) and high prevalence of osteopenia/osteoporosis (66.4%) in colorectal cancer survivors. No treatment-related significant risk factors of osteopenia and osteoporosis were found in this cross-sectional study. These results suggest that education about risks, means of prevention and screening for osteoporosis are not routinely discussed or implemented with long-term survivors of colorectal cancer. Clinicians should be aware of this prevalence of this vitamin D deficiency and osteopenia/osteoporosis in colorectal cancer survivors and new treatment strategies are necessary to reduce further osteopenia/osteoporosis risk in colorectal cancer survivors.

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