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JOURNAL CLUB ARTICLE

Optimizing Vitamin D Status to Reduce Colorectal Cancer Risk: An Evidentiary Review

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Vitamin D deficiency is common in the general public and in patients with cancer. Optimizing vitamin D intake is increasingly recognized in cancer risk reduction, particularly in decreasing colorectal cancer risk. Therefore, summarizing the current evidence to promote best practices related to vitamin D intake and colorectal cancer risk reduction is important. The objectives of this article are to examine the current evidence regarding the impact of vitamin D on colorectal cancer risk reduction and provide practice recommendations for clinicians. Relevant research articles from 2002–2008 were retrieved from multiple electronic databases. Reference lists of relevant articles also were searched manually. Twenty-five research reports were selected for this article: 4 randomized, controlled trials; 11 cohort or case-control studies measuring serum 25-OH-D levels; and 10 cohort studies reporting vitamin D intake. This review generated three themes: raising 25-OH-D levels to a vitamin D sufficient state (32–100 ng/ml) achieved colorectal cancer risk reduction, increasing the intake of vitamin D reduced colorectal cancer risk, and increasing vitamin D intake to 1,000 IU daily is safe and likely sufficient to raise serum 25-OH-D levels above 32 ng/ml to achieve colorectal cancer risk reduction. Several practice recommendations are suggested.

Cancer is one of the most dreaded diagnoses from a physiological, psychological, social, and spiritual standpoint. According to the American Cancer Society ([ACS], 2008), cancer is the second leading cause of death in the Untied States; about 1.5 million Americans were diagnosed with some form of cancer in 2008 and more than 500,000 died. In addition, the estimated overall cost of cancer care reached $219 billion in 2007 (ACS). Therefore, cancer prevention and risk reduction clearly are in the national interest. Healthcare providers in particular have a major responsibility in leading the fight against cancer by actively screening for cancer, treating cancer-predisposing conditions in a timely manner, and educating the public about cancer prevention (including directly modifiable risk factors). Vitamin D deficiency is considered one such risk factor for many types of solid organ cancers, such as colorectal cancer, breast cancer, and ovarian cancer (Garland et al., 2006).

Vitamin D deficiency is an epidemic health problem in the industrial world; an estimated 1 billion people have vitamin D deficiency (Cherniack, Levis, & Troen, 2008; Holick, 2007). In the United States, 25%–58% of adolescents and adults are deficient in vitamin D (Looker, Dawson-Hughes, Calvo, Gunter, & Sahyoun, 2002). Among patients with cancer, the prevalence of vitamin

At a Glance

- Vitamin D deficiency or insufficiency (less than 32 ng/ml or 80 nmol/L) is common in the general population and in patients with cancer.
- Current evidence suggests that optimizing serum 25-OH-D levels to the normal range of 32–100 ng/ml is associated with colorectal cancer risk reduction.
- Daily vitamin D intake of 1,000 IU is safe and likely sufficient to reduce colorectal cancer risk.

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D deficiency is much higher, approaching 90% (Everett, 2008; Hershman et al., 2006; Li et al., 2007; Maddipatla et al., 2007).

Since the late 1990s, studying vitamin D's effect on cancer has been of increasing interest. Ecological studies have shown that heightened sun exposure decreases internal solid organ cancers (Boscoe & Schymura, 2006; Grant, 2007; Tuohimaa et al., 2007). Researchers also have observed that higher intake of vitamin D from diet, supplements, or both is associated with a lower risk of colorectal and breast cancers (Garland et al., 2006; Lin et al., 2007; Robien, Cutler, & Lazovich, 2007). A meta-analysis of 18 randomized, controlled trials (RCTs) demonstrated that vitamin D supplementation is associated with decreased total mortality rates from life-threatening conditions such as cancer, cardiovascular disease, and diabetes mellitus (Autier & Gandini, 2007). Many studies have similarly demonstrated an inverse relationship between serum 25-OH-D levels and the risk of colorectal, breast, and prostate cancers (Garland et al., 2006). In addition, lower serum 25-OH-D levels are associated with higher overall mortality, colorectal cancer–specific mortality, and more advance-staged disease in breast cancer and colorectal cancer (Fakih & Sunga, 2006; Goodwin, Ennis, Pritchard, Koo, & Hood, 2008; Melamed, Michos, Post, & Astor, 2008; Ng et al., 2008; Palmieri, MacGregor, Girgis, & Vigushin, 2006; Sieg, Sieg, Dreyhaup, & Schmidt-Gayk, 2006).

The major research breakthrough demonstrating the direct cancer risk reduction by vitamin D intake was reported by Lappe, Travers-Gustafson, Davies, Recker, and Heaney (2007). Their RCT studied 1,179 postmenopausal women and found that taking 1,100 IU of vitamin D plus 1,400–1,500 mg of daily calcium for four years resulted in a 60%–77% overall cancer risk reduction. Following this report, the Canadian Cancer Society (2007) updated their vitamin D recommendation to 1,000 IU daily for typical adults during fall and winter months and year-round for adults at high risk for vitamin D deficiency. Subsequently, the Family Physicians Inquiries Network in the United States published a pivotal report in response to this research finding, suggesting that double-dose vitamin D lowers cancer risk in women older than age 55 (Schumann & Ewigman, 2007).

It has been shown that vitamin D increases the apoptosis in the colorectal epithelium, thereby reducing the risk of developing colorectal neoplasia (Holt et al., 2002, 2006). Indeed, many cell types, including colorectal epithelial cells, contain vitamin D receptors (VDRs) and express 1-α-hydroxylase. These cells are, therefore, able to convert the circulating 25-OH-D into active 1-25-OH-D metabolite, which, in turn, binds to the cells' own VDRs to produce an autocrine effect by inducing cell differentiation and inhibiting proliferation, invasiveness, angiogenesis, and metastatic potentials (Giovannucci, 2006). Among a large number of published research articles on the relationship between vitamin D and various cancers, vitamin D's effects on colorectal cancer risk reduction has been most widely studied and reported. Therefore, this evidentiary article will primarily focus on the vitamin D effect in colorectal cancer risk reduction with the goals of transforming scientific knowledge into clinical practice. The objectives are to examine the effect of vitamin D on colorectal cancer prevention and risk reduction and provide practical recommendations for clinicians to evaluate and treat vitamin D deficiency in patients, as well as optimize vitamin D status accordingly.

Definition of Terms

Vitamin D status, the prohormonal vitamin D representing the amount of vitamin D storage in the body, is measured by the serum 25-OH-D assay. Serum 25-OH-D levels less than 32 ng/ml (80 nmol/L) represent hypo-vitamin D, or vitamin D deficiency or insufficiency (Holick, 2007).

25-OH-D (25-hydroxyvitamin D): 25-hydroxyvitamin D, known as 25-hydroxycholecalciferol, is the main vitamin D metabolite circulating in plasma, consisting of 25-OH-D_2 or 25-OH-D_3, depending on its origin. 25-OH-D represents the vitamin D storage status in the human body (Quest Diagnostics, 2008).

1-25-OH-D (1-25-hydroxyvitamin D): In the kidney, 25-OH-D changes into an active hormonal form of vitamin D called 1-25-OH-D. The active form helps control blood levels of calcium and phosphate balance. 1-25-OH-D level is highly controlled and regulated by the parathyroid hormone (MedlinePlus Medical Encyclopedia, 2007a).

Confidence interval (CI): a range of values within which the population parameter is estimated to fall based on the statistic and the standard error (Munro, 2005)

Hazard ratio (HR): a measure of how often a particular event happens in one group compared to how often it happens in another group over time. In cancer research, HR = 1 indicates that no difference exists in survival between the two groups; HR more than or less than 1 indicates that survival is better in one of the groups (National Cancer Institute, 2008).

Interquartile range (IQR): the range of values extending from the 25th to the 75th percentile (Munro, 2005)

Odds ratio (OR): the probability of occurrence over the probability of nonoccurrence (Munro, 2005)

Parathyroid hormone (PTH): is secreted by the parathyroid glands to regulate the amount of calcium and phosphorous available in the blood. The role of PTH includes raising the level of calcium in the blood, decreasing the level of phosphorous in the blood, and increasing the amount of active vitamin D available in the body (MedlinePlus Medical Encyclopedia, 2007b).

Probability value (p value): in a statistical hypothesis test, the likelihood of getting the value of the statistic by chance alone (Munro, 2005)

Relative risk or risk ratio (RR): the risk given one condition versus the risk given another condition (Munro, 2005)

R^2 (variance): Squared multiple correlation is the amount of variance accounted for the dependent variable by a combination of independent variables (Munro, 2005).

Search Strategy

To retrieve the best evidence on vitamin D in colorectal cancer prevention and risk reduction, electronic searches were conducted in a variety of databases from 2002–2008 because, generally speaking, evidence from the most recent five-year period is considered most relevant to research. An Ovid search was carried out through Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE®, and CINAHL® by using keywords *vitamin D*, *25 hydroxyvitamin D*, or *cholecalciferol*; *colorectal neoplasm*; *clinical trial*; *cohort studies*; *case-controlled studies*; and *epidemiologic studies*. The PubMed database was searched using *vitamin D*, *colorectal neoplasm*, and *clinical trial*; *vitamin D*, *colorectal neoplasm*, and *cohort studies*; *vitamin D*, *colorectal neoplasm*, and *case-controlled studies*; and *vitamin D*, *colorectal neoplasm*,

and *epidemiologic studies*. In addition, manual searches were conducted on reference lists of relevant articles.

No systematic reviews or meta-analyses based on randomized trials were found. Thirty-five potential research reports were identified, including RCTs, cohort studies, case-control studies, and epidemiologic studies. The study interests regarding vitamin D and colorectal neoplasm consist of vitamin D intake from diet and supplements, sun exposure, serum 25-OH-D levels, vitamin D receptor polymorphism, and clinical trials with vitamin D plus calcium intervention.

Twenty-five articles were selected for this evidentiary review (see Table 1). The selection criteria were based on strengths of evidence grade: RCTs with vitamin D as the intervention (n = 4); cohort or case-control studies using serum 25-OH-D level measurement as the indicator variable reflecting vitamin D status to assess association with colorectal neoplasm (including colorectal adenomas and colorectal cancers) (n = 11); and cohort or case-control studies measuring vitamin D intake from diet, supplements, or both to examine the association with colorectal neoplasm (n = 10). Studies on adenomas or colorectal polyps also were selected because adenomas occur prior to cancer development, making adenomas the true indicator of colorectal cancer risk. Ecologic studies were not included, as these studies provide only suggestive associations between regions or seasons and sun exposure as the vitamin D proxy. Several studies based on VDRs as the main vitamin D variables also were not included because VDRs are not well understood and are probably less practical from a clinical perspective.

Analysis and Synthesis

The Rating System for Levels of Evidence (Melnyk & Fineout-Overholt, 2005) was used to grade the research studies selected for this evidentiary review. There are seven levels of evidence in this rating system, with level I representing evidence from a systematic review or meta-analysis through level VII representing evidence from expert opinion and/or consensus groups (Melnyk & Fineout-Overholt). Most studies in this review were rated as level II (one well-designed RCT) or level IV (well-designed case control and cohort studies). For discussion purposes, the studies are grouped into three categories based on the major variable of study interest: RCTs with vitamin D as an intervention, cohort or case-control studies measuring 25-OH-D levels as the primary variable, and cohort or case-control studies measuring vitamin D intake from diet and supplements.

Vitamin D as a Research Intervention in Randomized, Controlled Trials

Lappe et al. (2007) conducted a four-year, population-based, placebo-controlled, three-arm RCT with 1,179 postmenopausal women to examine the efficacy of calcium alone versus calcium plus vitamin D on cancer incidence of all types. Results revealed that the group taking 1,100 IU of vitamin D plus 1,400–1,500 mg of calcium daily had a 60% overall cancer risk reduction compared to the placebo group (risk ratio [RR] = 0.4, 95% confidence interval [CI] 0.2–0.82, p = 0.01). Excluding cancer cases in the first year yielded an even more dramatic reduction in risk of 77% (RR = 0.23, 95% CI 0.09–0.6, p < 0.005). Vitamin D plus calcium treatment accounted 5.5% of the overall variance (R^2 = 0.055), with the number needed to treat to prevent one case of cancer equaling 20 patients. No difference existed in toxicity profile among the three groups. The major limitations of this RCT are the short study duration of four years, relatively few cases of cancer diagnosis (a total of 50 cancer cases, 13 during the first year and 37 during the subsequent three years), and the fact that cancer incidence was the secondary outcome.

In contrast, the double-blind, placebo-controlled Women's Health Initiative (WHI) study with 36,282 postmenopausal women found that taking 1,000 mg of calcium plus 400 IU of vitamin D daily for seven years revealed no protective effect against colorectal cancer incidence as the secondary outcome (RR = 1.08, 95% CI 0.86–1.34, p = 0.51) (Wactawski-Wende et al., 2006). However, the nested study of 25-OH-D level measurement at baseline did show that higher 25-OH-D levels were associated with less colorectal cancer risk (odds ratio [OR] = 2.53 for the lowest quartile of less than 31 nmol/L compared with the highest quartile of 58 nmol/L or higher, p = 0.02).

The WHI study has been subjected to several criticisms as a result of vitamin D supplementation showing no protective effects against colorectal cancer risk. First, the vitamin D dose (400 IU per day) used in the study potentially was too low to raise 25-OH-D levels into a meaningful range for a colorectal cancer risk reduction because 400 IU per day did not correct the vitamin D deficient status (Holick & Giovannucci, 2006). Instead, it only raised the mean 25-OH-D level from baseline 42 nmol/L (16.8 ng/ml) to 47 nmol/L (18.8 ng/ml), whereas the suggested 25-OH-D level needed to decrease colorectal cancer risk is above 80 nmol/L (32 ng/ml) (Gorham et al., 2007). Second, a poor adherence rate of less than 50% existed among WHI study participants. Third, the concurrent use of overlapping estrogen therapy in the WHI study likely modified the effects of the calcium plus vitamin D regimen (Ding, Mehta, Fawzi, & Giovannucci, 2008). Ding et al. (2008) re-analyzed the primary data from the WHI study to focus on women concurrently taking supplemental estrogen. The hazard ratio (HR) of colorectal cancer for women concurrently taking calcium-vitamin D and estrogen was 1.5 (95% CI 0.96–2.33), which suggested increased risk. The HR of colorectal cancer for women taking calcium and vitamin D but concurrently assigned to the non-estrogen arm was 0.71 (95% CI 0.46–1.09), which indicated a possible protective benefit. The interaction between concurrent estrogen usage and calcium plus vitamin D supplementation was statistically significant (p = 0.02).

Two small RCTs examined the effects of calcium plus vitamin D on the epithelial cell proliferation from colorectal mucosa and polyps (Holt et al., 2002, 2006). Findings demonstrated that 400 IU of vitamin D plus 1,500 mg of calcium daily for six months decreased epithelial cell proliferation of the colorectal mucosa and colorectal polyp mucosa. Additionally, vitamin D plus calcium appeared to inhibit polyp formation. The anti-carcinogenic effect of vitamin D was supported by an in vitro study, as human colon cancer cells treated with vitamin D showed up-regulation of VDR and 25-hydroxyvitamin D-1-α-hydroxylase expression (Murillo, Matusiak, Benya, & Mehta, 2007). Previous case-control studies also have demonstrated that vitamin D increases

Table 1. Studies Researching Vitamin D Deficiency

STUDY	PURPOSE	DESIGN AND METHOD	SAMPLE AND SETTING	MAJOR FINDINGS	LEVEL OF EVIDENCE	CRITIQUE
Vitamin D as a Research Intervention in RCTs						
Holt et al., 2002	To examine the relationship between serum levels of 25-OH-D, 1-25-OH-D, and the indices of colorectal epithelium proliferation and differentiation	Three-arm RCT consisting of calcium (1,500 mg daily), calcium (1,500 mg) plus vitamin D (400 IU) daily, or 1-25-OH-D 0.25 mcg bid; duration was six months.	139 outpatients with history of polyps within three years from two hospitals in New York City	The calcium plus vitamin D group (adding baseline dietary vitamin D equaling the total of 800 IU per day) increased 25-OH-D levels by 44% to 37 ng/ml. Epithelial cell proliferation decreased as serum 25-OH-D increased, suggesting local autocrine effects on circulating 25-OH-D. Calcium appeared to enhance the effects of 25-OH-D.	II	The study provided the biologic explanation for CRC control from circulating serum 25-OH-D.
Holt et al., 2006	To study the effects of calcium plus vitamin D on colorectal adenoma mucosa changes measured by biomarkers	Two-arm RCT consisting of placebo or calcium (1,500 mg) plus vitamin D (400 IU) daily; duration was six months.	19 outpatients with small polyps (less than 9 mm) from the population of one New York City hospital	Calcium plus vitamin D significantly decreased the proliferative indices of colorectal polyps, increased the VDR staining, and strikingly decreased the MUC5AC mucin staining (a proliferative marker).	II	The study provided the biological explanation for CRC control effects of calcium plus vitamin D.
Lappe et al., 2007	To determine the efficacy of placebo, calcium alone, and calcium plus vitamin D in cancer incidence as the secondary outcome	Three-arm RCT consisting of placebo, calcium (1,400–1,500 mg), or calcium (1,400–1,500 mg) plus vitamin D (1,100 IU) daily; duration was four years.	1,179 community-dwelling postmenopausal women	Calcium plus vitamin D significantly increased 25-OH-D levels after 12 months of intervention (from 71.8 to 96 nmol/L); calcium plus vitamin D decreased cancer incidence by 60% (RR = 0.4, 95% CI 0.2–0.82, p = 0.01) over four years. If first year was excluded, calcium plus vitamin D decreased cancer incidence by 77% (RR = 0.23, 95% CI 0.09–0.6, p < 0.005).	II	Cancer incidence was not the primary end point. The four-year duration may not be long enough because of the latency period for cancer development.
Wactawski-Wende et al., 2006	Whether calcium (1,000 mg) plus vitamin D (400 IU) daily helps prevent CRC (the second outcome)	Two-arm RCT consisting of placebo or calcium (500 mg) plus vitamin D (200 IU) twice per day; duration was seven years.	36,282 nationwide postmenopausal women from the Women's Health Initiative study	Calcium plus vitamin D was effective in reducing CRC risks (HR = 1.08, 95%CI 0.96–1.34, p = 0.51), but the nested case-control analysis showed that higher baseline 25-OH-D levels had a trend of less CRC risk (OR = 2.53 for the lowest quartile of less than 31 nmol/L compared with the highest quartile of more than 58 nmol/L, p = 0.02).	II	Vitamin D at 400 IU per day may be too small to achieve a meaningful effect. The treatment adherence rate was low (less than 50%).
Dose Response Between Serum 25-OH-D Levels and CRC Risk						
Feskanich et al., 2004	To examine the risk of colorectal cancer in relation to serum vitamin D metabolites (25-OH-D and 1-25-OH-D)	Case-control cohort study	193 cases from the Nurses' Health Study; one CRC case matched with two health controls	Serum 25-OH-D levels were inversely associated with CRC risks, comparing the top quartile of 35.3–44.5 ng/ml to the bottom quintile of 14.9–17.4 ng/ml (OR = 0.53, 95% CI, 0.27–1.04, p = 0.02). No dose response existed between 1-25-OH-D levels and CRC risks.	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Freedman et al., 2007	To examine the relationship between serum 25-OH-D levels and cancer mortality	Cohort study drawn from the Third National Health and Nutrition Examination Survey	17,705 population-based sample (older than age 17) in the United States	Total cancer mortality was unrelated to baseline 25-OH-D levels. Baseline serum 25-OH-D levels of 80 nmol/L or greater were associated with a 72% risk reduction in CRC mortality (95% CI 0.32–0.89), compared with levels lower than 50 nmol/L (p = 0.02).	IV	The study failed to demonstrate causal effect because of a lack of RCT design.

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CI—confidence interval; CRC—colorectal cancer; HR—hazard ratio; HRT—hormone replacement therapy; OR—odds ratio; RCT—randomized, controlled trial; RR—risk ratio; VDR—vitamin D receptor

Note. Level of evidence II indicates evidence from at least one well-designed RCT; level IV indicates evidence from well-designed case-control and cohort studies.

Table 1. Studies Researching Vitamin D Deficiency *(Continued)*

STUDY	PURPOSE	DESIGN AND METHOD	SAMPLE AND SETTING	MAJOR FINDINGS	LEVEL OF EVIDENCE	CRITIQUE
Giovannucci et al., 2006	To assess vitamin D status with cancer incidence and cancer mortality	Cohort study of male health professionals in the United States; duration was 14 years.	47,800 men with 4,286 diagnosed with cancer; 2,025 died from cancer.	An increment of predicated 25 nmol/L of 25-OH-D levels significantly decreased CRC risk by 37% (RR = 0.63, 95% CI 0.48–0.83). For digestive system cancers, an increment of 25 nmol/L of predicted 25-OH-D level significantly reduced the cancer incidence by 43% (RR = 0.57, 95% CI 0.46–0.71), with a 45% reduction in cancer mortality (RR = 0.55, 95% CI 0.41–0.74).	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Grau et al., 2003	To assess the independent and joint effects of calcium and vitamin D status on colorectal advanced adenoma recurrence	Cohort study drawn from the Calcium Polyps Prevention Study	803 subjects with two sets of 25-OH-D levels from a multicenter study in the United States	Median 25-OH-D level was 29.1 ng/ml. Higher 25-OH-D (more than 29.1 ng/ml) and calcium acted jointly to decrease adenoma recurrence (RR = 0.71, 95% CI 0.57–0.89, p = 0.12).	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Jacobs et al., 2006	To assess the relationship among serum 25-OH-D levels, dietary intake of vitamin D, and colorectal adenoma recurrence.	Cohort study drawn from the Ursodeoxycholicacid Multi-Clinic Trial	211 adenoma cases and 508 controls; outpatients were from multiple clinics in Arizona.	The association between 25-OH-D levels and adenoma recurrence was stronger for women with higher 25-OH-D levels (33 ng/ml) (OR = 0.59, 95% CI 0.3–1.16) versus women with low levels (17.2 ng/ml) than for men (OR = 0.95, 95% CI 0.6–1.49). An overall moderate, nonsignificant, inverse association existed between 25-OH-D levels and adenoma.	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Miller et al., 2005	To examine whether calcium and vitamin D are associated with increased apoptosis in normal rectal biopsy tissue	Cross-sectional study	498 outpatients (174 adenoma patients, 324 nonadenoma patients) from an East Coast hospital	High calcium intake (more than 739 mg per day) increased the rectal apoptosis in patients with adenoma (OR = 3.4, 95% CI 0.9–12.9). Higher serum 25-OH-D levels (more than 34.9 ng/ml) were strongly associated with the rectal epithelium apoptosis scores in patients free of adenoma (OR = 2.6, 95% CI 1.1–6.2), but slightly lower in adenoma patients (p = 0.13) compared with lowest tertile (less than 20.9 ng/ml).	IV	The study provided the biological explanation for CRC risk reduction. The study failed to demonstrate causal effect because of a lack of RCT design.
Otani et al., 2007	To investigate the association between serum 25-OH-D levels and the risk of CRC	Nested case-control study	38,373 population-based sample from Japan with 375 cancer cases and 750 controls	Serum 25-OH-D level was not significantly associated with CRC risks in men and women. A suggestive inverse relationship existed in men. The lowest quintile of 25-OH-D (22.9 versus 32.1 ng/ml for men, 18.7 versus 27 ng/ml for women) was associated with an elevated risk of rectal cancer in men (OR = 4.6, 95% CI 1–2) and women (OR = 2.7, 95% CI 0.94–7.6).	IV	The study failed to demonstrate causal effect because of a lack of RCT design.

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CI—confidence interval; CRC—colorectal cancer; HR—hazard ratio; HRT—hormone replacement therapy; OR—odds ratio; RCT—randomized, controlled trial; RR—risk ratio; VDR—vitamin D receptor

Note. Level of evidence II indicates evidence from at least one well-designed RCT; level IV indicates evidence from well-designed case-control and cohort studies.

Table 1. Studies Researching Vitamin D Deficiency *(Continued)*

STUDY	PURPOSE	DESIGN AND METHOD	SAMPLE AND SETTING	MAJOR FINDINGS	LEVEL OF EVIDENCE	CRITIQUE
Peters et al., 2004	To study the association of vitamin D levels with colorectal adenoma risk and the effects of calcium and HRT in relation to vitamin D on adenoma risk.	Nested case-control study drawn from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	772 cases and 777 controls from a multi-center study	Women had a significantly decreased risk for advanced adenoma (OR = 0.27, 95% CI 0.11–0.69; p = 0.0002), comparing the highest quintile of 25-OH-D levels (36.6–72.8 ng/ml) with the lowest quintile (6.8–19.2 ng/ml). No risk reduction was observed in men. HRT increased 25-OH-D levels, but no effect on adenoma risk reduction.	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Sieg et al., 2006	To assess the relationship among serum 25-OH-D levels, colorectal adenoma, and CRC risk	Case-control study	203 adenoma cases, 98 CRC cases, and 239 controls	Patients with CRC had significantly lower 25-OH-D levels compared to controls (winter was 15 ng/ml versus 23 ng/ml, p = 0.001; summer was 21 ng/ml versus 29 ng/ml, p = 0.0007). Patients with adenoma had significantly lower 25-OH-D levels in winter (24 ng/ml versus 29 ng/ml, p = 0.01). 25-OH-D levels showed an inverse correlation to CRC stages.	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Wu et al., 2007	To study the association between serum 25-OH-D levels and the risk of colorectal cancer	The National Health Professional Study, a nested case-control study, and pooled analysis from the Nurses' Health Study	18,225 healthcare professionals in the United States	Higher 25-OH-D levels significantly reduced colon cancer risk, comparing the highest (39.4 ng/ml) with the lowest quintile (18.4 ng/ml) (OR = 0.46, 95% CI 0.24–0.89, p = 0.005). Pooled analysis showed decreased CRC and colon cancer risks, compared the highest to lowest quintile (CRC was OR = 0.66, 95% CI 0.42–1.05, p = 0.01; colon cancer was OR = 0.54, 95% CI 0.34–0.86, p = 0.002).	IV	The study failed to demonstrate causal effect because of a lack of RCT design.
Vitamin D Intake and CRC Risk						
Hartman et al., 2005	To evaluate the association between calcium and vitamin D intake and recurrence of adenomatous polyps	Cohort study drawn from the Polyps Prevention Trial; duration was four years.	2,079 participants from a population-based sample in the United States	Total vitamin D intake was inversely associated (although weakly) with adenoma recurrence, fifth quintile (11.7 mcg per day) versus first quintile (3.35 mcg per day) (OR = 0.84, 95% CI 0.62–1.13, p = 0.03). Supplemental calcium and vitamin D were inversely associated with adenoma recurrence (calcium user was OR = 0.82, 95% CI 0.68–0.99; vitamin D user was OR = 0.82, 95% CI 0.68–0.99). Vitamin D was slightly stronger in preventing multiple polyp recurrences (OR = 0.73, 95% CI 0.53–0.99).	IV	No 25-OH-D level. The study was not a RCT design and lacked causal effect.
Kesse et al., 2005	To study the association between intake of dietary calcium, phosphorus and vitamin D, dairy products, and the risk of adenomatous polyps and CRC	Cohort study with a duration of 6.9 years	74,524 population-based French women aged 40–65 years	The relative risk of adenoma and CRC decreased with high calcium intake. No association was found between dietary vitamin D intake and risk of colorectal tumors.	IV Null finding	90% of subjects had low D intake of less than 400 IU per day. The study was not a RCT design and lacked causal effect.

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CI—confidence interval; CRC—colorectal cancer; HR—hazard ratio; HRT—hormone replacement therapy; OR—odds ratio; RCT—randomized, controlled trial; RR—risk ratio; VDR—vitamin D receptor

Note. Level of evidence II indicates evidence from at least one well-designed RCT; level IV indicates evidence from well-designed case-control and cohort studies.

Table 1. Studies Researching Vitamin D Deficiency *(Continued)*

STUDY	PURPOSE	DESIGN AND METHOD	SAMPLE AND SETTING	MAJOR FINDINGS	LEVEL OF EVIDENCE	CRITIQUE
Lin et al., 2005	To assess the intake of calcium and vitamin D in relation to CRC risk.	Cohort study	36,976 postmenopausal women from the Women's Health Initiative sample	Total calcium and vitamin D intake (from diet and supplements) were not associated with the risk of CRC.	IV Null finding	Low median vitamin D intake of 271 IU per day was unlikely to be meaningful. No 25-OH-D level. The study was not a RCT design and lacked causal effect.
Martinez et al., 2002	To assess whether calcium and vitamin D intake from diet and supplements is associated with risk of adenoma recurrence	Cohort study drawn from the Wheat Bran Fiber Trial	1,304 men and women with polyps larger than 3 mm removed within three months in Arizona	Dietary calcium intake and total calcium intake decreased adenoma recurrence. Dietary vitamin D (174 IU per day) was inversely (but weakly) associated with adenoma recurrence. No association was revealed for supplemental sources of vitamin D (400 IU per day) and total vitamin D intake (455 IU).	IV	Dose cutoffs for analysis are likely too low to detect differences. No 25-OH-D level. The study was not a RCT design and lacked causal effect.
McCullough et al., 2003	To examine the association between intake of calcium, vitamin D, and dairy products and the risk of CRC	Cohort study drawn from the Cancer Prevention Study II nutritional study; duration was four years.	60,866 men and 66,883 women from a population-based sample in the United States	Higher total calcium intake from diet and supplements was associated with a marginally lower risk for CRC (for highest versus lowest quintiles, RR = 0.87, 95% CI 0.67–1.12, p = 0.02). Supplemental calcium was more effective (RR = 0.69, 95% CI 0.49–0.96, 500 mg per day versus none). Total vitamin D intake from diet and supplements was inversely associated with CRC risk (high quintile of more than 525 IU per day versus low quintile of 110 IU per day; RR = 0.8, 95% CI 0.62–1.02, p = 0.02), particularly in men (RR = 0.71, 95% CI 0.51–0.98, p = 0.02).	IV	For the effect of vitamin D intake, calcium intake, and dairy product intake on CRC risk, no 25-OH-D level was presented. The study was not a RCT design and lacked causal effect.
Mizoue et al., 2008	To investigate whether vitamin D intakes are associated with CRC risk	Case-control study	836 CRC cases and 861 controls from two university hospitals in Japan	High calcium decreased CRC risk. Vitamin D intake (high quintile 488 IU per day for women, 532 IU per day for men) was non-significantly inversely associated with CRC risk (p = 0.12). High calcium plus high vitamin D plus high sun exposure had the greatest inverse association with CRC risk (RR = 0.38, 95% CI 0.21–0.68, p = 0.001).	IV	For vitamin D intake, calcium intake and sun exposure on CRC risk, no 25-OH-D level was presented. The study was not a RCT design and lacked causal effect.
Oh et al., 2007	To examine calcium and vitamin D intake in relation to distal colorectal adenoma risk	Cohort study	48,115 women from the United States taking part in the Nurses' Health Study	Total calcium intake was weakly associated with reduced distal colorectal adenoma risk. Total vitamin D intake was weakly associated with reduced risk for distal colorectal adenomas (RR= 0.79, 95% CI 0.63–0.99; p = 0.07), but more strongly with distal colon adenoma risk (RR = 0.67, 95% CI 0.52–0.87, p = 0.004).	IV	For the affect of vitamin D intake and calcium intake on distal colorectal adenomas, no 25-OH-D level was presented. The study was not a RCT design and lacked causal effect.

(Continued on next page)

CI—confidence interval; CRC—colorectal cancer; HR—hazard ratio; HRT—hormone replacement therapy; OR—odds ratio; RCT—randomized, controlled trial; RR—risk ratio; VDR—vitamin D receptor

Note. Level of evidence II indicates evidence from at least one well-designed RCT; level IV indicates evidence from well-designed case-control and cohort studies.

Table 1. Studies Researching Vitamin D Deficiency *(Continued)*

STUDY	PURPOSE	DESIGN AND METHOD	SAMPLE AND SETTING	MAJOR FINDINGS	LEVEL OF EVIDENCE	CRITIQUE
Park et al., 2007	To examine the associations of calcium and vitamin D intake from foods and supplements with CRC risk	Cohort study	191,011 population-based multiethnic sample in the western United States	Total calcium intake significantly reduced CRC risk in men and women. Total vitamin D intake reduced CRC risk in men only (RR = 0.72, 95% CI 0.51–1, p = 0.03). High dietary vitamin D reduced CRC risk for women (RR = 0.78, 95% CI 0.63–0.96), particularly for those not taking supplements (RR = 0.69, 95% CI 0.52–0.93, p = 0.03). Dairy products reduced CRC risk, particularly for those not taking supplements (for men, RR = 0.77, 95% CI 0.59–1.01; for women, RR = 0.66, 95% CI 0.49–0.89).	IV	For vitamin D intake, calcium intake, and dairy products' affect on CRC risk, no 25-OH-D level was presented. The study was not a RCT design and lacked causal effect.
Slattery et al., 2004	To determine the effect of intake of calcium, vitamin D, and dairy products on rectal cancer, and the effect of the BSM I (a type of VDR) and poly-A VDR polymorphisms on rectal cancer risk	Case-control study	2,306 rectal cancer cases and 2,749 controls from a population based in the western United States	Women's rectal cancer risk was reduced with a high quintile of vitamin D intake of more than 8.3 mcg per day (OR = 0.52, 95% CI 0.32–0.85), high intake of low-fat dairy products (OR = 0.61, 95% CI 0.39–0.94), and high calcium intake (OR = 0.39, 95% CI 0.24–0.64). High levels of sunshine exposure for participants younger than age 60 reduced rectal cancer risk (OR = 0.62, 95% CI 0.42–0.93).	IV	For dietary calcium, vitamin D, sunshine, and dairy products' affect on rectal cancer risk, no 25-OH-D level was presented. The study was not a RCT design and lacked causal effect.
Theodoratou et al., 2008	To evaluate the associations between CRC risk and the intake of vitamin D and calcium; to investigate whether any association is mediated via the VDR pathway	Case-control study	A population-based sample in Scotland with 2,070 CRC cases and 2,793 controls	Dietary vitamin D intake and total vitamin D intake were significantly, inversely associated with CRC risk, with a 20%–23% reduction for high (6–8.31 ug/d) versus low (2.51–2.76 mcg/d). Additional meta-analyses of serum 25-OH-D from previous studies showed an inverse association between 25-OH-D and CRC risk (OR = 0.7, 95% CI 0.56–0.87), suggesting the association was mediated through the vitamin D binding to the VDR.	IV	The study failed to demonstrate causal effect because of a lack of RCT design.

CI—confidence interval; CRC—colorectal cancer; HR—hazard ratio; HRT—hormone replacement therapy; OR—odds ratio; RCT—randomized, controlled trial; RR—risk ratio; VDR—vitamin D receptor

Note. Level of evidence II indicates evidence from at least one well-designed RCT; level IV indicates evidence from well-designed case-control and cohort studies.

colorectal epithelium apoptosis (Diaz, Paraskeva, Thomas, Binderup, & Hague, 2000; Miller et al., 2005).

An effective dosage of vitamin D to raise 25-OH-D levels above 80 nmol/L (32 ng/ml) is critical in achieving cancer risk reduction. Previous investigators have demonstrated a dose-response relationship between cancer risk and 25-OH-D levels. Quantitative pooled analyses from cohort studies reveal that correction of vitamin D deficiency to an optimal level of 33 ng/ml or higher (82.5 nmol/L) is associated with a 50% reduction in colorectal cancer risk (Gorham et al., 2007), while a level of 52 ng/ml or higher (130 nmol/L) is associated with a 50% beast cancer risk reduction (Garland et al., 2007). In the study by Lappe et al. (2007), vitamin D intake of 1,100 IU per day raised 25-OH-D levels from a baseline of 71.8 nmol/L to 96 nmol/L. However, in the WHI study, vitamin D intake of 400 IU per day was too low to raise 25-OH-D levels above 80 nmol/L to achieve any meaningful cancer risk reduction. Given these mixed results, a RCT in a large sample using an effective vitamin D dose to keep 25-OH-D level within the range of 32–100 ng/ml (measured twice a year in both winter and summer) over 10 years is needed to provide the strongest evidence of vitamin D's long-term effects in cancer risk reduction.

Dose Response Between 25-OH-D Level and Colorectal Cancer Risk

Eleven studies based on cohort and case-control research designs examined the relationship between serum 25-OH-D levels and colorectal cancer risk. Seven of the studies showed various degrees of risk reduction for colorectal cancer and four

for colorectal adenoma at higher serum 25-OH-D levels. The major limitations of the studies were that they were unable to demonstrate causal effects between vitamin D and colorectal cancer risk and that the 25-OH-D levels were mostly one-time measurements, which may not accurately represent vitamin D status because 25-OH-D levels fluctuate with seasonal changes.

Seven studies evaluated the effects of serum 25-OH-D levels on colorectal cancer risk. A predictive model based on a cohort study indicated that every 25 nmol/L increase in 25-OH-D levels produces a 37% colorectal cancer reduction (RR = 0.63, 95% CI 0.48–0.83) (Giovannucci et al., 2006). Wu et al. (2007) conducted a nested control study from the cohort of the Health Professional Follow-Up Study (HPFS), pooled the data with the Nurse Health Study (NHS) for analysis, and found a significant inverse relationship for colon cancer risk between the highest and the lowest quintile of 25-OH-D levels in the HPFS cohort (fifth quintile = 39.4 ng/ml and first quintile = 18.4 ng/ml, OR = 0.46, 95% CI 0.24–0.89, p = 0.005). The pooled analysis with the NHS showed significantly decreased risks for total colorectal and colon cancer comparing the highest to the lowest quintile of 25-OH-D levels (total colorectal cancer OR = 0.66, 95% CI 0.42–1.05, p = 0.01; colon cancer OR = 0.54, 95% CI 0.34–0.86, p = 0.002). The third study of the NHS cohort alone (Feskanich et al., 2004) revealed that 25-OH-D levels were inversely associated with colorectal cancer risk (fifth quintile versus first quintile OR = 0.53, 95% CI 0.27–1.04, p = 0.02). For women older than 60 years of age, the OR for colorectal cancer risk from the highest quintile of 25-OH-D levels was 0.35 (95% CI 0.14–0.87, p = 0.006), but no dose-response relationship was found between colorectal cancer risk and level of 1-25-OH-D (the hormonal form of vitamin D). Similarly, a case-control study by Sieg et al. (2006) supported that higher 25-OH-D levels were associated with significantly lowered colorectal cancer risk.

Otani, Iwasaki, Sasazuki, Inoue, and Tsugane (2007) conducted a population-based, nested-control study of 25-OH-D levels and colorectal cancer risk in Japan and found the lowest quartile of 25-OH-D level was associated with an elevated risk of rectal cancer in men (lowest quartile of less than 23 ng/ml versus highest quartile of more than 32.1 ng/ml, OR = 4.6, 95% CI 1–20) and women (lowest quartile of less than 18.7 ng/ml versus highest quartile of more than 27 ng/ml, OR = 2.7, 95% CI 0.94–7.6). However, Freedman, Looker, Chang, and Graubard (2007) examined the effect of 25-OH-D levels on cancer mortality from the cohort of the Third National Health and Nutrition Examination Survey and found no relationship between 25-OH-D levels and total cancer mortality. However, 25-OH-D levels of 80 nmol/L (32 ng/ml) or higher were associated with a 72% reduction in colorectal cancer mortality (95% CI 32–89) compared with 25-OH-D levels of less than 50 nmol/L (p = 0.02). Ng et al. (2008) analyzed the influence of prediagnosis serum 25-OH-D levels on colorectal cancer–specific mortality from the cohort of the HPFS and the NHS and reported that 25-OH-D levels significantly reduced the overall mortality (lowest quartile of less than 18.8 ng/ml versus highest quartile of more than 29ng/ml, HR = 0.52, 95% CI 0.29–0.94, p for trend = 0.02). A statistically nonsignificant trend existed toward improved colorectal cancer-specific mortality (HR = 0.61, 95% CI 0.31–1.19, p for trend = 0.23)

Patient Education Resources on Vitamin D Deficiency

Mayo Clinic: www.mayoclinic.com/health/vitamin-d/NS_patient-vitamind

Merck Manuals: www.merck.com/mmhe/sec12/ch154/ch154j.html

Vitamin D Council: www.vitamindcouncil.org

WebMD: www.webmd.com/food-recipes/features/are-you-getting-enough-vitamin-d?page=2&print=true

Video Clips on Vitamin D Deficiency

Vitamin D and cancer prevention: www.youtube.com/watch?v=1PsyaYNX1dw&feature=channel

What's a vitamin D deficiency? www.youtube.com/watch?v=emjCzaHtSrg

Four other studies examined serum 25-OH-D levels and colorectal adenoma risk. Jacobs et al. (2006) examined the sample cohort originating from the Ursodeoxycholicacid Trial for adenoma prevention and found a moderate, non-significant inverse association between 25-OH-D levels and adenoma recurrence. Interestingly, Miller et al. (2005) revealed that higher 25-OH-D levels were associated with higher rectal epithelium apoptosis for patients with or without adenomas. Peters et al. (2004) conducted a nested case-control study within the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial. Comparing the highest quintile (greater than 36.6 ng/ml) with the lowest quintile (19.2 ng/ml or lower) of 25-OH-D levels, the risk for advanced adenoma was decreased by 73% in women (OR = 0.27, 95% CI 0.11–0.69, p = 0.0002), but the risk was not decreased in men (OR = 1.1, 95% CI 0.6–2.05, p = 0.85). Again, serum 1-25-OH-D was not associated with advanced adenoma risk. Grau et al. (2003) assessed the cohort from the Calcium Polyp Prevention Trial and found a joint effect of 25-OH-D levels and calcium on adenoma recurrence. Only subjects with a 25-OH-D level above the median of 29.1 ng/ml and taking 1,500 mg of calcium daily demonstrated a statistically significant reduction for adenoma recurrence (RR = 0.71, 95% CI 0.57–0.89, p = 0.01).

In summary, serum 25-OH-D levels, which represent vitamin D status, have consistently revealed an inverse relationship with colorectal cancer and colorectal adenoma risks. The lower the level, the higher the risk. The levels of 25-OH-D in Grau et al. (2003), Jacobs et al. (2006), Miller et al. (2005), and Peters et al. (2004) demonstrated a significant colorectal cancer or adenoma risk reduction in the range of 27–39.4 ng/ml, with a median of 33 ng/ml. Such a level is well within the normal range of 32–100 ng/ml for 25-OH-D levels.

Vitamin D Intake and Colorectal Cancer Risk

Ten studies measured the effect of vitamin D intake from diet and supplementation on colorectal cancer risk using cohort or case-control designs. Although level IV evidence is assigned for these studies, the measurement of vitamin D intake may not truly reflect vitamin D status because many factors affect such status, including age, obesity, physical activity, skin color, sunshine exposure, and smoking history (Holick, 2007). Moreover, the amount of vitamin D intake cannot be determined

accurately because food survey questionnaires were used to estimate the amount of vitamin D intake for individuals.

Seven of the 10 studies revealed favorable findings regarding higher vitamin D intake and colorectal tumor risk reduction. For example, one population-based case-control study in Scotland found that vitamin D intake from diet and supplementation significantly reduced colorectal cancer risk (Theodoratou et al., 2008). Another case-control study conducted in Japan reported that the combination of high vitamin D, calcium intake, and high sun exposures resulted in the greatest colorectal cancer risk reduction compared to each factor alone (Mizoue et al., 2008). Similarly, two additional studies demonstrated that high levels of vitamin D intake, increased consumption of low fat dairy products, or high levels of sunshine exposure decreased colorectal cancer risk (McCullough et al., 2003; Slattery et al., 2004). Interestingly, Park et al. (2007) examined vitamin D intake and colorectal cancer risk from a multiethnic cohort sample in California and Hawaii and found an inverse association between total vitamin D intake and colorectal cancer risk in men (RR = 0.72, 95% CI 0.51–1, p = 0.03) but not in women (RR = 0.89, 95% CI 0.63–1.27, p = 0.8). However, women who had high vitamin D intake from foods showed a significantly lowered risk (RR = 0.78, 95% CI 0.93–0.96), which was even more evident in women who did not take supplements (RR = 0.69, 95% CI 0.52–0.93, p = 0.03). Two studies assessed the effect of vitamin D intake on colorectal adenomas. One examined the NHS cohort and found that total vitamin D intake was weakly associated with reduced risk of combined distal colorectal adenomas (RR = 0.79, 95% CI 0.63–0.99, p = 0.07), and more strongly associated with distal colon adenoma risk reduction (RR = 0.67, 95% CI 0.52–0.87, p = 0.004) (Oh, Willett, Wu, Fuchs, & Giovannucci, 2007). Another study investigated vitamin D intake on polyp recurrence from the cohort of the Polyps Prevention Trial and determined that total vitamin D intake was inversely (although weakly) associated with adenoma recurrence, comparing the fifth to the first intake quintiles (OR = 0.84; 95% CI 0.62–1.13, p = 0.03; for vitamin D supplementation, OR = 0.82, 95% CI 0.68–0.99) (Hartman et al., 2005). Overall, vitamin D appeared to be more effective in preventing multiple recurrences of polyps (OR = 0.73, 95% CI 0.53–0.99) (Hartman et al.).

Conversely, three studies did not find an inverse relationship between vitamin D intake and colorectal cancer risk. The first study examined the relationship between vitamin D intake and the risk of colorectal adenoma and colorectal cancer among a large group of French women (N = 74,524) with no association found between colorectal tumor and vitamin D intake after almost seven years of follow-up (Kesse, Boutron-Ruault, Norat, Riboli, & Clavel-Chapelon, 2005). However, this sample had a low consumption of vitamin D, with the 90th percentile of 4.34 mcg per day (less than 400 IU per day). A second study conducted in the United States reported similar findings when analyzing vitamin D intake in the large WHI female cohort (N = 36,976) (Lin et al., 2005). The median vitamin D intake of 271 IU per day also was low in this sample (Lin et al., 2005). Likewise, Martinez, Marshall, Sampliner, Wilkinson, and Alberts (2002) assessed the effect of vitamin D intake from dietary and supplemental sources on colorectal adenoma recurrence among 1,304 men and women who had polyps removed within three months of study entry. They were unable to detect any significant impact of vitamin D intake on polyp recurrence after an average follow-up time of three years; however, the vitamin D dose for cutoff in this analysis also was low, about 400 IU per day. Therefore, low doses of vitamin D intake likely contributed to the non-significant results in colorectal cancer risk reduction in all three studies.

In summary, the studies of vitamin D intake and colorectal tumor risk reveal inconsistent results. Vitamin D intake may only represent a portion of the overall vitamin D resource availability and is, therefore, unable to reflect true vitamin D status. In addition, vitamin D intake was estimated from food questionnaires, which were subject to measurement errors and recall biases. Moreover, different studies adopted different food questionnaires. Despite these limitations, higher vitamin D intake generally decreased colorectal tumor risk.

Safety, Cost, and Benefits

Vitamin D intoxication (hypercalcemia and hyperphosphatemia) occurs when 25-OH-D levels reach 150 ng/ml (375 nmol/L) (Holick, 2007). However, as described earlier, 1,100 IU per day of vitamin D revealed no difference in toxicity profile compared with placebo (Lappe et al., 2007). In Hathcock, Shao, Vieth, and Heaney (2007), subjects taking 10,000 IU per day of vitamin D for up to five months did not demonstrate toxic effects. In light of these findings, many experts are urging the Food and Nutrition Board of the Institute of Medicine to update the original vitamin D recommendation from 1997 because it no longer is supported by the evidence. The U.S. Food and Drug Administration (FDA) recommendations for vitamin D are 200 IU per day for ages 19–50, 400 IU per day for age 51–70, and 600 IU per day for ages 71 and older.

Studies suggest that vitamin D intake should be around 1,000 IU per day to provide benefits for bone health and cancer risk reduction (Lappe et al., 2007; Vieth et al., 2007). Considering that more than 50% of Americans and about 80% of cancer survivors use dietary supplements without medical advice (Miller et al., 2008; Velicer & Ulrich, 2008), an evidence-based vitamin D recommendation will help guide the general public regarding safety and quality-of-life outcomes. Grant, Garland, and Gorham (2007) estimated that 1,000 IU per day of vitamin D would result in a 7%–9% absolute cancer reduction in the United States and a 14%–20% cancer reduction in Western Europe. In short, the overall health benefits of vitamin D greatly outweigh the potential risks (Grant & Garland, 2008). In fact, to date, no health risk associated with daily vitamin D intake of 1,000–2,000 IU has been reported.

Regarding the financial savings associated with increased vitamin D intake, the cost-to-benefit ratio can be calculated based on Lappe et al. (2007), which noted that treating 20 people prevents one cancer case over four years. The per-person cost of 1,000 IU per day of vitamin D is about $20 per year, or $80 for four years per person, which translates into $1,600 for 20 people over four years. In 2008, the overall cost for one cancer case was about $152,520, calculated from the estimated 1,437,180 cancer cases with a cost of $219.2 billion based on ACS (2008). Dividing the cost for one cancer case in 2008 ($152,520) by four years equals $38,130, meaning that for every $1,600 spent on vitamin D, a potential cost-saving of $38,130 in cancer treatment exists. This yields an excellent cost-benefit ratio of 1:24 just from cancer alone.

Suggested Recommendations

Healthcare providers play important roles in disease prevention, health promotion, and education. Because vitamin D deficiency is a widespread public health issue linked to cancer and other health risks, healthcare providers should not ignore this easily correctable condition. The FDA recommendations for vitamin D were set by the Institute of Medicine in 1997, but results from the WHI suggest that these recommendations are ineffective in preventing vitamin D deficiency as well as decreasing the risk for osteoporotic fractures and colorectal cancer development (Jackson et al., 2006; Wactawski-Wende et al., 2006). Higher vitamin D dosages of 700–1,100 IU per day used in previously cited RCTs resulted in 25-OH-D levels in the 80–100 nmol/L range with subsequent reductions in fracture and cancer risks (Bischoff-Ferrari et al., 2005; Lappe et al., 2007). Previous studies also have clearly revealed that vitamin D status (25-OH-D level) and vitamin D intake are inversely associated with cancer

Table 2. Treatment Recommendations for Vitamin D Deficiency

RECOMMENDATION	RATIONALE
Encourage patients to take 1,000 IU per day of vitamin D plus 1,200–1,500 mg of daily calcium if 25-OH-D levels are not available.	These supplemental amounts have been shown to reduce overall cancer risks, including risks for colorectal cancer (Gorham et al., 2007; Lappe et al., 2007) and fracture risks (Bischoff-Ferrari et al., 2005).
Screen 25-OH-D levels twice a year (near the end of summer and near the end of winter) for high-risk individuals.	Subclinical vitamin D deficiency (less than 32 ng/ml) is common in the general population, and the prevalence among patients with cancer and individuals with osteoporosis or osteopenia is alarmingly high (Everett, 2008; Hershman et al., 2006; Holick, 2007; Li et al., 2007; Lips et al., 2006; Maddipatla et al., 2007). Because 25-OH-D levels fluctuate with seasons because of sun exposure, measuring these levels twice a year provides more accurate assessment of vitamin D status (Freedman et al., 2007). Parathyroid hormone (PTH) levels also should be checked for individuals with osteopenia or osteoporosis and patients with metastatic bone disease. Vitamin D deficiency should be corrected prior to initiating bisphosphonate therapy to prevent hypocalcemia (Wang-Gillan et al., 2006; Yazbeck et al., 2007). Individuals at highest risk of vitamin D deficiency include those with the following conditions or circumstances: cancer; osteoporosis and osteopenia; chronic kidney disease; liver disease; fibromyalgia; migraine headaches; gastrointestinal malabsorption, which often occurs after gastrectomy or gastric bypass procedures; Crohn disease; celiac spruce disease; people living in northern latitudes; older adults; young children; people who are homebound; people who have darker skin color; people who are obese or inactive; or people who are taking certain medications such as anticonvulsants, glucocorticoids, HIV/AIDS treatments, and antirejection drugs after organ transplantation (Holick, 2007).
Correct vitamin D deficiency through vitamin D repletion.	Raising 25-OH-D levels within a range of 32–100 ng/ml results in numerous positive health outcomes, including stronger bones, colorectal cancer risk reduction, and increased muscle strength to reduce falls, which is particularly important for older adults (Bischoff-Ferrari et al., 2006). For every 40 IU (1 mcg) of vitamin D_3, serum 25-OH-D levels increase by about 1 nmol/L (0.4 ng/ml) (Heaney et al., 2003). Very low levels of 25-OH-D may require prescription strength vitamin D (50,000 IU in D_2 form in the United States). For 25-OH-D levels less than 20–32 ng/ml, consider 50,000 IU of vitamin D_2 weekly for four to five weeks; for 25-OH-D levels less than 15–20 ng/ml, consider 50,000 IU of vitamin D_2 weekly for eight weeks (Lyman, 2005); and for 25-OH-D levels less than 15 ng/ml, consider 50,000 IU of vitamin D_2 twice a week for five weeks (Adams et al., 1999). Recheck 25-OH-D levels one to two weeks after repletion, with repetition of repletion based on the level-dose recommendations if 25-OH-D levels do not increase above 32 ng/ml.[a]
Maintain vitamin D at the sufficient state with 25-OH-D levels in the range of 32–100 ng/ml; however, levels of 50–100 ng/ml are optimal for most patient populations.[a]	Without vitamin D maintenance after repletion, 25-OH-D levels will drop in two to four months because vitamin D has a half-life of one to two months (Vieth, 1999). The optimal 25-OH-D level of 50–100 ng/ml is preferred for colon cancer and breast cancer risk reduction (Garland et al., 2007; Gorham et al., 2007). Alternatively, Cannell and Hollis (2008) proposed that, for patients with serious illnesses associated with vitamin D deficiency such as cancer, heart disease, multiple sclerosis, diabetes, autism, and a host of other illnesses, doses should be sufficient to maintain year-round 25-OH-D levels from 55–70 ng/ml. Recommend a maintenance dose of 1,000 IU of vitamin D_3 daily (Lyman, 2005). Because poor adherence to daily dosing is common, an alternative is to prescribe 50,000 IU of vitamin D_2 once or twice per month (e.g., once a month in summer and twice per month in winter). Many patients prefer this approach with fewer pills. For those reluctant to take pills, recommend vitamin D rich foods, such as oily fish (e.g., salmon, tuna, canned sardines, mackerel), fortified foods, cod liver oil, and Shiitake mushrooms (Holick, 2007).
Advise concurrent calcium intake of 1,200 mg daily for men and premenopausal women, and 1,500 mg daily for postmenopausal women and individuals with osteoporosis or osteopenia.	Calcium and vitamin D work jointly to promote strong bones and reduce cancer risk, as evidenced by the fact that most randomized, controlled trials have incorporated vitamin D and calcium as the intervention for cancer and fracture risk reduction (Bischoff-Ferrari et al., 2005; Lappe et al., 2007).

[a] For individuals with chronic granulomatous disorders, such as sarcoidosis and some lymphomas, 25-OH-D levels should be kept at lower range of 20–30 ng/ml because of higher sensitivity to circulating 25-OH-D (Holick, 2007), primarily from the unregulated production of calcitriol (1-25-OH-D) from activated macrophage in sarcoidosis associated with a risk of hypercalcemia (Conron et al., 2000; Sharma, 2000). Individuals with primary hyperparathyroidism and chronic kidney disease associated vitamin D deficiency should be referred to a specialist in lieu of clinical management.

risks, particularly for colorectal cancer (Garland et al., 2006). Therefore, optimizing vitamin D intake provides "win-win" benefits of correcting vitamin D deficiency, promoting bone health, and reducing colorectal cancer risks. Based on currently available evidence, Table 2 outlines treatment recommendations for vitamin D deficiency.

Implications and Conclusion

Although government healthcare agencies have not adopted any vitamin D recommendations for cancer risk reduction, current evidence is substantial and compelling and supports the role of vitamin D in reducing colorectal cancer risk. Nationally and internationally, many experts are urging healthcare agencies and international food and nutritional boards to recommend an effective allowance for vitamin D intake (Veith et al., 2007). Ideally, more definitive evidence of vitamin D on any cancer risk reduction should be obtained through large, population-based, longitudinal RCTs with adequate doses of vitamin D as interventions. However, such trials are expensive, and sales of vitamin D, a rather low-cost supplement, cannot generate enough profits to offset the trial cost. However, the Vitamin D/Calcium Polyp Prevention Study (2004–2017), a double-blinded, four-arm RCT with 2,200 subjects, currently is underway to evaluate the effects of placebo, calcium (1,200 mg per day), vitamin D (1,000 IU per day), and calcium plus vitamin D (1,200 mg plus 1,000 IU per day) on colorectal neoplasia risk reduction, but the result will not be available until after the study's completion. (For more information on the trial, visit http://clinicaltrials.gov/ct2/show/NCT00153816.) In the meantime, vitamin D debates will continue regarding optimal vitamin D intakes, optimal vitamin D status, emerging roles of vitamin D, and so forth, adding the complexity of future vitamin D researches (Beres, 2008).

Considering that more than 50% of Americans and 80% of cancer survivors are taking dietary supplements without clinical advice (Miller et al., 2008; Velicer & Ulrich, 2008), and acknowledging the overall safety profile of vitamin D and its wide range of health benefits, recommending that patients take 1,000 IU of vitamin D daily is reasonable and practical and clinicians should make every effort to promote and maintain optimal vitamin D status in their patients. Above all, given that patient care is a multifaceted process, clinicians must consider the current research evidence, their patients' condition and preferences, and their own experiences and judicious clinical judgment in addressing the need for vitamin D supplementation.

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Journal Club Discussion Questions

This article has been identified as appropriate for a journal club. When you read this article, think about how you would change your current practice regarding screening and managing vitamin D deficiency in your patients. See the Evidence-Based Practice column in the February 2009 *Clinical Journal of Oncology Nursing* (Vol. 13, No. 1, pp. 109–112) on how to implement and participate in journal clubs. Photocopying of this article for discussion purposes is permitted.

1. What is the clinical practice question the authors are trying to answer?
2. Is the purpose of the article described clearly?
3. Is the literature review comprehensive and are major concepts identified and defined?
4. Are the clinical recommendations supported by evidence? What are they?
5. Do you currently screen patients for vitamin D deficiency? How do the clinical recommendations compare to your current practice?
6. What practice change recommendations will you make based on the evidence presented in this article? Who should get screened for vitamin D deficiency? When, where, and how often should they be screened? How should someone be managed if deficient?
7. What patient education materials are available on this topic?