Shedding Light on Serum Vitamin D Concentrations and the Risk of Rarer Cancers

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Abstract: Cancer is a broad term for many disparate diseases with different etiologies, commonly classified by affected organ site. This review summarizes the published evidence from prospective cohort studies examining the associations between vitamin D, measured as serum 25-hydroxyvitamin D (25OHD) concentrations, and the risk of rarer cancer sites including pancreatic, non-Hodgkin lymphoma, ovarian, endometrial, kidney, gastric and esophageal cancer. Overall, evidence from prospective cohort studies provides little support for a protective association between adequate or higher serum 25OHD concentrations and risk of these rarer cancer sites. Additionally, controversy persists concerning a potential increased risk of pancreatic cancer associated with serum 25OHD levels >100 nmol/L due to conflicting results reported by two large prospective pooling projects.

Keywords: 25-hydroxyvitamin D, Bladder cancer, Cancer, Cohort, Endometrial cancer, Esophageal cancer, Gastric cancer, Kidney cancer, Nested case-control study, Non-Hodgkin lymphoma, Ovarian cancer, Pancreatic cancer, Prospective studies, Vitamin D.

INTRODUCTION

Adequate vitamin D, the sunshine vitamin, is needed for bone health, the primary indication on which the Dietary Reference Intake (DRI) for vitamin D is based [1]. However, the role of vitamin D in preventing other disease outcomes, or in preserving overall optimum health, is less certain [1]. In determining adequate intake for specific nutrients, the lesson learned from the story of Goldilocks and the three bears should be kept in mind: vitamin concentrations should not be too low or too high, as both are associated with harm. The challenge for vitamin D is to find the amount of vitamin D that is "just right" for optimum health. The Institute of Medicine (IOM) report on DRIs for calcium and vitamin D considered serum 25-hydroxyvitamin D (25OHD) concentrations of 50 nmol/L (20 ng/mL) as adequate. In the IOM committee's extensive review, no consistent health benefit was observed for serum 25OHD concentrations above 75 nmol/L (30 ng/mL); in addition, the committee indicated that there was evidence of adverse health effects associated with levels exceeding 125 nmol/L (50 ng/mL). The IOM committee concluded that consensus guidelines are needed to set optimum clinical cut-points for classifying individuals as deficient or having excessive vitamin D. Some of the evidence for health concerns comes from studies of 25OHD concentrations and rarer cancer outcomes.

Finding the "just right" amount for vitamin D intake and 25OHD concentrations is critical to avoid harm, especially in the prevention setting where the goal is preserving health rather than treating illness. The relatively brief history of research for effective cancer chemoprevention has shown that high doses of micronutrients may be associated with harm rather than benefit [2]; thus caution with excessive dosing is necessary. Vitamin A and beta-carotene interventions among smokers increased the risk of lung cancer rather than preventing it [3, 4]. High doses of folic acid have been shown to increase, rather than decrease, the risk of adenomatous polyps [5]. Selenium and vitamin E supplementation in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) resulted in a significantly increased prostate cancer risk compared to placebo [6]. Given these unfortunate results in cancer prevention trials testing supplements as chemopreventive agents, it is common sense to be wary of high dose supplementation for any micronutrient [7].

Vitamin D is the latest vitamin to be touted for potential health benefits beyond its well established role in skeletal health. Controversy persists regarding the amount of vitamin D required for optimum health. The IOM concluded that there was no evidence of benefit beyond maintaining skeletal health by avoiding deficient levels; additionally, the IOM noted that the published evidence suggests "there may be reason for concern" for serum concentrations in excess of 125 nmol/L (50 ng/mL) [1]. With skyrocketing sales of vitamin D supplements and a reported sales volume of 425 million for vitamin D in 2009 [8], determining what amount of vitamin D is "just right" is urgently needed.

Preventing cancer is an important goal encompassed in achieving optimum health. Cancer is a broad term that reflects a collection of diseases, classified most commonly according to site of origin, with a wide array of causes with great variation in rates of occurrence. This review focuses on the associations between vitamin D and rarer cancer outcomes, where published evidence is more limited than with common cancers such as colorectal cancer. Hypothesis generating studies, such as ecological correlation studies, are not considered. Emphasis in this review is placed on prospective studies, especially those with pre-diagnosis measures of 25OHD concentrations. Serum 25OHD concentrations reflect the multiple sources of vitamin D – the body's production of vitamin D with sun exposure, food sources, and supplements. Prospective studies also avoid the concern that the presence of disease influences 25OHD concentrations through either decreased dietary intake or sun exposure as a result of illness, especially for those cancers that are often diagnosed at advanced stages such as pancreatic and ovarian cancer. Few clinical trials of vitamin D supplementation and cancer outcomes have been done, and those that have been completed or are currently being conducted have limited power to examine the associations between vitamin D and rarer cancer outcomes. Rarer cancers are largely "orphan" diseases when it comes to cancer prevention trials, as few, if any, studies are adequately powered to examine outcomes for cancers other than the most common cancer sites such as breast, prostate or colorectal cancers. For example, the ongoing VITamin D and OmegA-3 Trial (VITAL) has a recruitment goal of 20,000 men and women to determine the effects of 2000IU of vitamin D (in the form of cholecalciferol) and omega-3 fatty acids on cancer and cardiovascular disease [9]. The number of total cancer cases is a primary outcome; the numbers of breast, colorectal and prostate cancers, but not other rarer cancers, are secondary outcomes.

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Rarer cancer sites investigated in serum-based prospective studies in association with vitamin D include pancreatic cancer, lymphoma, ovarian cancer, endometrial cancer, kidney cancer, gastric cancer, and esophageal cancer. Studies cited in this review were identified through Medline searches including the name of the cancer site and search terms of vitamin D or 25OHD and from review of reference lists of identified studies.

PANCREATIC CANCER

The evidence concerning the association between vitamin D and pancreatic cancer is inconsistent. A case-control study nested (200 cases and 400 controls) within a long-term follow-up of the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, conducted among Finnish male smokers, observed increasing risk of pancreatic cancer with increasing 25OHD concentrations (P-for-trend = 0.006). The cut-point for the highest fifth of the distribution was 65.5 nmol/L, reflecting the lower overall 25OHD levels observed in the general population in Finland compared to other parts of the world [10]. A subsequent nested case-control study conducted within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial (184 cases and 368 controls) observed a risk of pancreatic cancer in the highest (concentrations >82.3 nmol/L) compared to the lowest quintile (concentrations ≤ 45.9 nmol/L) in excess of 1.00; however, the odds ratio (OR) was not statistically significant (OR 1.45; 95% CI 0.66-3.15) [11]. Subsequently the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers was conducted, including nested case-control studies from eight cohorts, to investigate the association between serum 25OHD concentrations and subsequent pancreatic cancer [12]. The pooled analysis included 952 incident pancreatic cases and 1,333 controls from studies conducted in the United States, Finland and China. Compared to concentrations <25 nmol/L, an increased risk of pancreatic cancer was observed for those with serum concentrations of 25OHD ≥ 100 nmol/L (OR 2.24; 95% CI 1.22-4.12); however, there was no evidence of a dose response trend. Excluding the cases from two of the cohorts with previously published results [10, 11], the OR for the highest category compared to the lowest category was unchanged but no longer statistically significant (OR 2.23; 95% CI 0.82-6.08) [12]. A subsequent pooled study, with five cohorts that were different from those published as part of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, all based in the United States, was conducted and included 451 cases and 1,167 controls. Examining those with 25OHD concentrations considered sufficient (≥ 75 nmol/L) compared to those with levels < 50 nmol/L, the OR was 0.71 (95% CI 0.52-0.97). Among those with 25OHD concentrations of 50 to <75 nmol/L, a range considered adequate (DRI report), the risk of pancreatic cancer was similar (OR 0.75; 95% CI 0.58-0.98) to that observed for those with sufficient levels. In an analysis that used the same cut-points as defined by the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers, the adjusted OR among those with 25OHD concentrations >100 nmol/L compared to those with 25OHD concentrations from 50 to <75 nmol/L was 1.01 (95% CI 0.63-1.62) [13]. A study by Weinstein *et al*. [14] suggests that levels of vitamin D binding protein (DBP) may impact the association between serum 25OHD concentrations and pancreatic cancer risk. Analyzing data from the ATBC study, Weinstein *et al*. observed the increased risk of pancreatic cancer was primarily observed among men with serum DBP below the median and in the highest fourth of 25OHD concentrations compared to those in the lowest fourth of 25OHD concentrations (OR 5.01; 95% CI 2.33-10.78).

One study showed a lower risk of pancreatic cancer at concentrations that have been recommended as adequate for skeletal health (25OHD > 75nmol/L) but no association with pancreatic cancer for concentrations >100nmol/L compared to those

with concentrations <50 nmol/L [13]. Overall, the evidence to date from prospective cohort studies suggests that there is no benefit and potentially harm at higher concentrations of 25OHD above 100 nmol/L.

NON-HODGKIN LYMPHOMA

A nested case-control study (270 incident cases and 538 controls) of the association between serum 25OHD concentrations and the development of lymphoid cancer was conducted within the ATBC trial follow-up cohort of Finnish male smokers [15]. Among individuals with 25OHD concentrations ≥59.5 nmol/L, no increase or decrease in the risk of all lymphoid cancers combined was observed compared to individuals with 25OHD concentrations ≤40 nmol/L (OR 0.95; 95% CI 0.65-1.40). In addition, no statistically significant associations were observed between 25OHD and specific types of lymphoid cancer [15]. Subsequently, the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers examined the association between 25OHD concentrations and non-Hodgkin lymphoma (NHL), pooling across 10 cohorts from three continents, including 1,353 NHL cases and 1,778 controls [16]. No statistically significant associations were observed at either high or low serum 25OHD concentrations by categorized subtype (diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic/small lymphocytic lymphoma; or other/not otherwise specified) or for all combined. A subsequent cohort study of predicted (not measured) plasma 25OHD concentrations and NHL cases, of which 1,064 incident cases were analyzed, conducted within the Nurses Health Study, found no statistically significant association between predicted 25OHD concentrations and NHL risk [17]. Thus, prospective studies overall do not suggest an association between vitamin D and the risk of lymphoid cancers overall or NHL specifically.

OVARIAN CANCER

The first prospective study of 25OHD concentrations and ovarian cancer was conducted drawing cases (n=224) from three cohorts: the Nurses Health Study (NHS); the Nurses Health Study II (NHSII), and the Women's Health Study (WHS) [18]. Compared to controls (n=603), no statistically significant association was observed between 25OHD concentrations and ovarian cancer. Similarly, a prospective study with 170 incident cases and 373 controls, pooling across two cohorts (New York University Women's Health Study and the Northern Sweden Health and Disease Study), also observed no association between 25OHD concentrations and the risk of ovarian cancer [19]. Further, a nested case-control study conducted within the Finnish Maternity Cohort [20], matching cases diagnosed within 10 years of serum sampling (n=201) to two controls each, showed no statistically significant excess risk of ovarian cancer among those in the lowest fifth of the 25OHD distribution compared to those in the highest fifth of the distribution (25OHD ≥ 53.1 nmol/L) (OR 1.8; 95% CI 0.9-3.5). The largest study is the pooling project of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers [21] with 516 cases and 770 controls drawn from seven prospective studies. Overall, in the Consortium study, no statistically significant associations were observed across a wide range of serum 25OHD concentrations and the risk of ovarian cancer. In conclusion, evidence from a wide range of international studies does not support an association between serum 25OHD and ovarian cancer.

ENDOMETRIAL CANCER

The association between serum vitamin D concentrations and the risk of endometrial cancer was examined in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers [22]. Pooling across seven prospective cohort studies, the association was examined among 830 cases and 992 controls. No statistically

significant associations between circulating levels of 25OHD and risk of endometrial cancer were observed either overall or in subgroups defined by body mass index, age at diagnosis, ever use of oral contraceptives or hormone replacement therapy.

KIDNEY CANCER

Pooling across eight prospective cohorts, the association between serum 25OHD and kidney cancer was examined in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers [23]. The study included 775 cases matched to 775 controls. A statistically significant decreased risk of kidney cancer was observed among females with concentrations ≥75 nmol/L compared to those with adequate concentrations defined as 50 to <75 nmol/L (OR 0.31; 95% CI 0.12-0.85); however, this finding was based on only 14 cases in the high category and there was no evidence of a dose response relationship. No statistically significant associations were observed for the renal cell carcinoma subtype or among men. Overall, the authors concluded that the evidence did not support an association between 25OHD concentrations and the risk of kidney cancer.

BLADDER CANCER

The association between serum 25OHD and bladder cancer has been examined in one cohort study, the ATBC Cancer Prevention Study [24], conducted among male Finnish smokers. Within this cohort, 250 incident bladder cases were identified and matched to 250 controls. Compared to those with serum 25OHD concentrations ≥ 50 nmol/L, those with levels of <25, 25 to <37.5, and 37.5 to <50 nmol/L had statistically significantly elevated ORs of 1.73 (95% CI 1.03-2.91), 1.81 (95% CI 1.05-3.14) and 1.76 (95% CI 1.02-3.02), respectively. To date, this is the only published prospective study examining the association between serum vitamin D and bladder cancer.

ESOPHAGEAL AND GASTRIC CANCER

A nested case-control study embedded in the General Population Trial of Linxian conducted in China observed an increased risk of esophageal squamous cell carcinomas (ESCC) associated with higher 25OHD concentrations for men but not women [25]. Specifically, among men in the highest fourth of the distribution of serum 25OHD (>51.6 nmol/L), an increased risk of ESCC was observed (hazard ratio (HR) 1.77; 95% CI 1.16-2.70) compared to men in the lowest quartile (≤20.3 nmol/L), with a statistically significant linear trend of increased risk from low to high concentrations (P_{trend}=0.003). No statistically significant trends in risk were observed for gastric cancer.

Esophageal and gastric cancers were also examined in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. A nested case-control study was conducted pooling across eight prospective cohort studies [26], including two Asian cohorts. A total of 1,065 cases and 1,066 controls were included in the study, with esophageal and gastric cancers combined in the analyses. Overall, no statistically significant association was observed between circulating 25OHD concentrations and upper gastrointestinal cancer. Results were similarly null for squamous and adenocarcinoma of the esophagus and for the cardia and non-cardia subtypes of gastric cancer. Among Asians, however, statistically significant decreased risks of upper gastrointestinal cancer were observed among those with 25OHD concentrations <25nmol/L, 25 to <37.5nmol/L, and 37.5 to <50 nmol/l compared to those with concentrations of 50 to <75 nmol/L (<25 nmol/L: OR 0.53; 95% CI 0.31-0.91; 25 to <37.5 nmol/L: OR 0.50, 95% CI 0.31-0.80; 37.5 to <50 nmol/L: OR 0.51; 95% CI 0.32-0.82).

SUMMARY

Prospective cohort studies provide little support for a protective role of vitamin D in the development of some of the rarer cancer sites, including pancreatic, ovarian, endometrial, kidney, upper gastrointestinal cancers and NHL. No association, either beneficial or harmful, was observed for any of the cancer sites for the range of 25OHD concentrations defined as adequate for skeletal health by the recent IOM report on DRI for calcium and vitamin D. Controversy persists for possible harm with respect to pancreatic cancer risk associated with higher concentrations of 25OHD (levels >100 nmol/L (40 ng/mL) [10, 12]).

Reliance on a single assessment of 25OHD concentrations is a limitation for many of the prospective studies included in this review, especially given the seasonal fluctuation of serum vitamin D concentrations. A study in Norway observed a correlation of 0.8 for serum 25OHD assessed one year apart for subjects in the placebo group of a vitamin D intervention study [27]. The authors concluded that similar to studies of single measures of blood pressure and cardiovascular outcomes, their study provides "support for use of a single 25OHD measurement to predict future health outcomes." The authors also examined the association within a long term cohort with multiple 25OHD measurements over a 14 year period. The correlation coefficient, taking into account the month of blood sampling, was 0.42 [27]. As reported in the article by Zelenuich-Jacquotte *et al.*, intraclass correlations for serum 25OHD concentrations of 0.78 (95% CI 0.64-0.88) and 0.72 (95% CI 0.62-0.80) were observed among women sampled annually over two to three years [22]. Thus, overall, a single 25OHD measurement appears to be a reasonable surrogate for longer term exposure.

Clinical trials are frequently lauded as the highest level of evidence in the hierarchical model of evidence-based medicine. For rarer cancer sites, that level of evidence is unlikely to be generated due to the large sample size required to have adequately powered studies. Well-designed clinical trials with appropriate vitamin D dosing, verification of serum concentrations achieved, and adequate duration of intervention are some of the additional challenges to evaluating the effect of vitamin D on rarer cancer outcomes. The VITAL trial [9] mentioned previously does not include rarer cancer sites in their list of clinical outcomes; the sample size of 20,000 is too small to evaluate the effect of vitamin D supplementation on rare cancer sites. The Women's Health Initiative, though not adequately powered to assess the effect of calcium plus vitamin D supplementation on rare cancers, did report on all individual cancer outcomes that occurred among the 36,282 women randomized to receive either 400IU vitamin D3 with 1,000 mg elemental calcium or placebo [28]. Serum 25OHD concentrations were not examined in the trial and, thus, the authors urged caution in interpreting the results of this study. In the Women's Health Initiative trial, total invasive cancer incidence and mortality were not reduced with supplementation. Among the rarer cancers reviewed in this publication, no reduction in risk associated with supplementation was observed. Only one site, bladder cancer, had a statistically significant weighted P value with a small excess risk of 1.24 observed for urinary cancers overall associated with calcium and vitamin D supplementation.

In summary, review of the currently available data assessing the association between 25OHD concentrations and the risk of rarer cancer sites does not support the hypothesis of benefit from supplementing beyond that needed to achieve adequate levels to maintain skeletal health.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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