Meta-analysis of Vitamin D Sufficiency for Improving Survival of Patients with Breast Cancer

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Abstract. *Background/Aim: To determine whether higher serum 25-hydroxyvitamin D [25(OH)D] at diagnosis is associated with longer survival of patients with breast cancer. Materials and Methods: A meta-analysis was performed of five studies of the relationship between 25(OH)D and mortality from breast cancer. A pooled hazard ratio was calculated using a random-effects model. The Der Simonian-Laird test was used to assess homogeneity. Results: Higher serum concentrations of 25(OH)D were associated with lower case-fatality rates after diagnosis of breast cancer. Specifically, patients in the highest quintile of 25(OH)D had approximately half the death rate from breast cancer as those in the lowest. Conclusion: High serum 25(OH)D was associated with lower mortality from breast cancer. Serum 25(OH)D in all patients with breast cancer should be restored to the normal range (30-80 ng/ml), with appropriate monitoring. Clinical or field studies should be initiated to confirm that this association was not due to reverse causation.*

There were approximately 234,580 new cases and 40,030 deaths from breast cancer in the United States in 2013 (1). Breast cancer is the most common cancer in women worldwide, with 1.7 million new cases and approximately one-half million deaths in 2012 (2). While most studies have focused on the relationship between vitamin D and incidence of breast cancer, only a few studies have investigated the possible relationship between serum 25-hydroxyvitamin D 25(OH)D status and cancer survival rates (3-7). The purpose of this study was to pool the results of known studies of the association between 25(OH)D status and breast cancer survival.

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Materials and Methods

A PUBMED search was conducted by two investigators for observational studies of serum 25(OH)D and risk of breast cancer performed between 1966-2010. The search was performed by using the terms ("vitamin D" or "cholecalciferol" or "calcidiol" or "calcitriol" or "25-hydroxyvitamin D"), and "epidemiology") and "human" as medical subject heading (MeSH) terms and words in the abstract, combined with the subject terms "breast neoplasms", "cancer", "survival" and "mortality". Articles were included if they were published in medical journals, were prospective or historical follow-up studies and reported survival or fatality rates according to quantiles of serum 25(OH)D. A total of 77 studies were identified during the literature review (Figure 1). Seventy studies were excluded after reviewing the abstracts. Two studies were excluded because they investigated the relationship between 1,25 dihydroxyvitamin D [1,25(OH)$_2$D] and breast cancer risk (8, 9). Five studies that reported hazard ratios (HRs) for mortality from breast cancer by quantiles of serum 25(OH)D were identified and eligible for inclusion (3-7).

Statistical analysis. The most adjusted age-adjusted hazard ratios comparing the lowest with the highest category of serum 25(OH)D concentration were obtained from each study. A pooled HR comparing the lowest with the highest quantile of serum 25(OH)D concentration was calculated using the Observed-Expected (O-E) and variance method for combining studies, an application of the Peto method for HRs (10). The overall O-E and variance were calculated using the individual HRs from each study and their 95% confidence intervals (11).

The *p*-value for the overall summary HR was calculated using a Z-score, where the numerator was the natural logarithm of the pooled HR and the denominator was the standard error of the natural logarithm of the pooled HR. This is a standard method for calculating the p-value using Peto's Assumption-free Method (12). HRs comparing the highest with the lowest quantiles for each study are displayed in a forest plot (13, 14). The DerSimonian-Laird statistic, using a random effects model, was used to assess inter-study heterogeneity among studies (15). The calculations were performed using Rev Man 5 (Oxford, UK: The Cochrane Collaboration).

Dose−response gradient. To provide a pooled estimate of the dose−response relationship between serum 25(OH)D and mortality, the average of the median or mid-point for each quantile from each study was calculated, as well as the average of the HR for each quantile. The highest quantile was used as the reference group for each study. If a
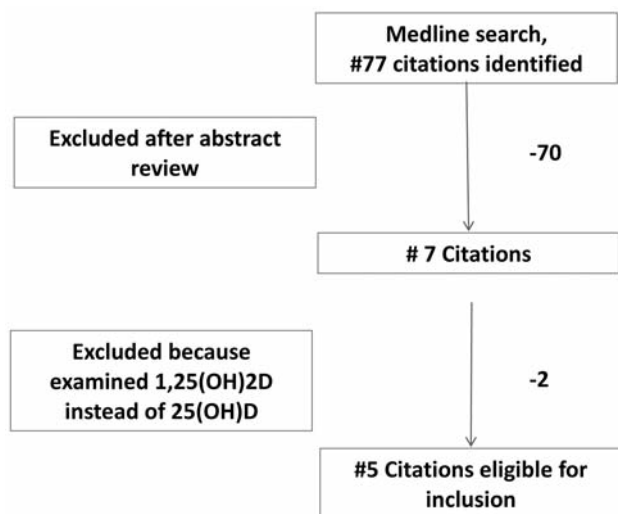
Figure 1. *Systematic flow chart of literature review.*

Figure 2. *Hazard ratio for death comparing the highest and lowest quantiles in each study, with 95% confidence intervals, and summary hazard ratio.*

study reported HRs using the lowest quantile as the reference category, the highest quantile was used as the reference group by obtaining the inverse of the HR of each quantile from that study. Ninety-five percent confidence intervals (95% CIs) for the average HRs were also calculated by using the average of the lower and upper 95% CIs from each quantile from each study. Computations were performed using SAS, Version 9.2 (SAS Institute, Cary, NC , USA).

Results

Five eligible studies were identified by the literature search, which is summarized in Figure 1. For breast cancer, serum 25(OH)D had a strong preventive effect against mortality. Of the five studies performed on the relationship between serum 25(OH)D and breast cancer mortality, three found a statistically significant reduction in mortality with increasing 25(OH)D concentrations (4-6). One study found a beneficial effect that did not reach statistical significance (7), while the fifth study found a beneficial effect in the age-adjusted but not multivariate analysis (3).

Individuals with higher serum concentrations of 25(OH)D had substantially lower fatality rates (Table I). Of the five studies, three found that serum 25(OH)D in the highest quantile was associated with substantially lower fatality rates than serum 25(OH)D in the lowest quantile (Figure 2) (4-6), and two found a trend in the same direction (3, 7). The overall pooled HR summarizing the estimated risk in the lowest compared to the highest category of 25(OH)D across all studies of breast cancer mortality was 0.56 (95% CI=0.4-0.7, $p<0.0001$) for women in the highest *vs.* the lowest category of serum 25(OH)D concentration (Figure 2). These results were homogenous across all studies (DerSimonian-Laird chi-square=4.46, $p=0.35$). The results were approximately the same using a fixed effects model.
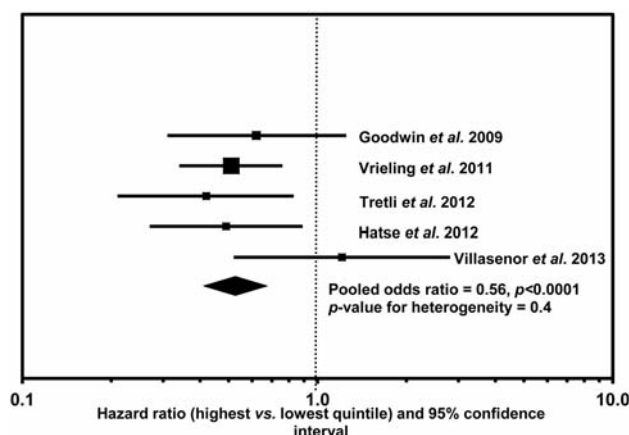
There was a strong linear, inverse dose–response relationship between serum levels of 25(OH)D and breast cancer fatality rates (Figure 3), with serum 25(OH)D accounting for 97% of the variance in case-fatality rates (Figure 3). A funnel plot revealed no strong indication of publication bias (Figure 4).

Discussion

Higher serum 25(OH)D concentrations were associated with lower fatality rates in patients with breast cancer. Patients with the highest concentration of 25(OH)D had approximately half the fatality rate compared to those with the lowest concentration.

While there has been considerable interest in the beneficial role of vitamin D and its metabolites in the prevention of colonic, breast, and other adenocarcinomas, there have been only a few studies on the association of vitamin D status at the time of diagnosis on survival of patients with breast cancer (3-7). Much research that has been carried out has shown very promising results (4-7).

The mechanisms by which vitamin D metabolites may prevent cancer may also explain the improved survival in patients with cancer who have higher serum 25(OH) D levels at the time of diagnosis (16). According to the vitamin D cancer prevention hypothesis, cancer occurs in several distinct phases that can be explained by a theoretical model termed the Disjunction-Initiation-Natural selection-Overgrowth-Metastasis-Involution-Transition (DINOMIT) model (16). Although this model has been applied primarily in the context of cancer prevention, several of the later stages that occur in vitamin D deficiency, such as Initiation, Natural Selection, Overgrowth, and Metastasis might help account for the effect of vitamin D metabolites on existing tumors. According to this hypothesis, the growth of a

Table I. *Characteristics of studies of serum 25-hydroxyvitamin D and breast cancer prognosis, ICD-CM Code 174, according to PubMed search, 1966-2013.*

| First author	Year	Study design	Length of follow-up (years)	Adjustment	Number of events/patients	25(OH)D Quantile (ng/ml)	Hazard ratio	95% Confidence interval	
								Lower	Upper
Goodwin (7)	2009	PC	11.6	Age, tumor stage, lymph node involvement, estrogen receptor status	106/512	<20	1.6	0.96	2.4
						20-28.8	0.98	0.57	1.69
						>28.8	1.0	-	-
Vrieling (6)	2011	PC	5.8	Age, metastasis, diabetes lymph node involvement, season of blood draw, estrogen receptor status, mode of detection, nodal status	183/1295	<14	1.55	1.0	2.39
						14-22	0.72	0.45	1.17
						>22	1.0	-	-
Tretli (5)	2012	RC	20	Sex, age, season of blood draw	82/251	<18.4	1.00	-	-
						18.4-24.7	0.60	0.33	1.09
						24.8-32.4	0.43	0.22	0.82
						>32.4	0.41	0.22	0.78
Hatse (4)	2012	PC	4.7	Age, BMI, tumor size, estrogen receptor status, grade	64/1800	<30	1.00	-	-
						>30	0.49	0.27	0.89
Villasenor (3)	2013	PC	9.2	Age	36/585	<20	1.00	-	-
						20-30	0.75	0.38	1.48
						>30	0.62	0.31	1.27

PC: Prospective cohort; RC: retrospective cohort.
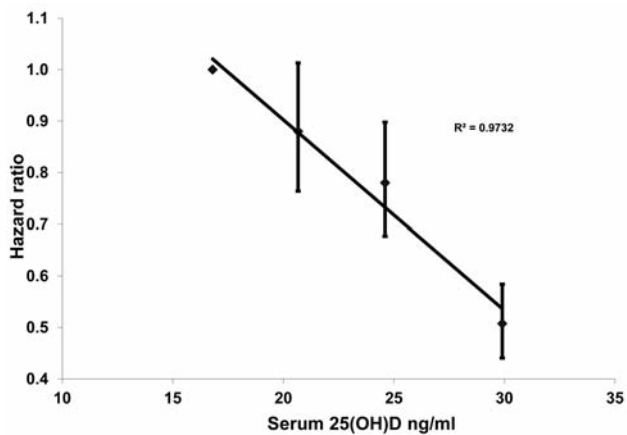
Figure 3. *Overall dose−response relationship between serum 25-hydroxyvitamin D and death from breast cancer, with coefficient of determination, all studies combined.*
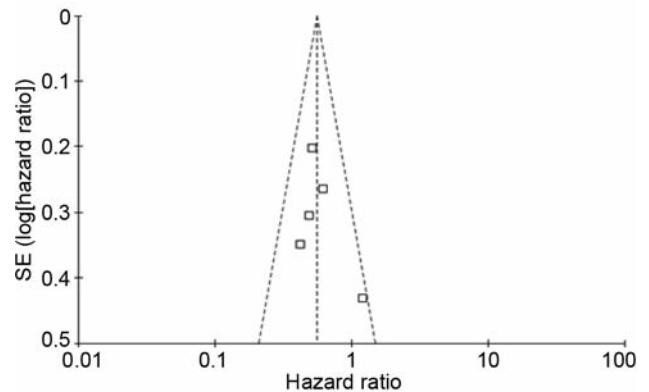

Figure 4. *Hazard ratios and their standard errors of their logarithms, all studies (Funnel plot).*

tumor may be arrested at almost any point in the DINOMIT model by restoring a high serum 25(OH)D concentration in the organism, resulting in up-regulation of E-cadherin and restoration of a well-differentiated state (16).

Laboratory studies have demonstrated anticancer effects of vitamin D metabolites on three critical phases in the development of breast tumors: differentiation, apoptosis, and angiogenesis. It is possible that the association of serum 25(OH)D with survival depends on maintaining differentiation, promoting apoptosis, and inhibiting angiogenesis. These are all known function of vitamin D metabolites (16).

On the other hand, the results of the present study could have resulted from reverse causation. It is possible that in the more serious cases, the serum 25(OH)D concentration was reduced and these were also the cases that resulted in death early in their natural history. If that were so, serum 25(OH)D

could be a biomarker for severity of cancer, rather than a factor that caused longer survival. This possibility could be ruled-out by performance of a clinical trial. There is one clinical trial of a reasonable dose of vitamin D (1000 IU) with calcium that showed a 77% reduction in incidence of all combined invasive cancer, including breast cancer (17). A clinical trial should be performed using the upper-level dose recommended by the National Academy of Sciences, which is 10,000 IU/day of vitamin D_3 (18).

In the meantime, no laboratory study to our knowledge has shown that tumors can reduce the serum 25(OH)D concentration. The death rate from cancer is also much lower in areas of the US with high solar UVB irradiance than those with lower irradiance (19), which cannot be accounted for by reverse causation. There is a similar association on a worldwide basis (20). These studies suggest it might be prudent for patients with breast cancer to have their serum 25(OH)D measured and repleted to concentrations in the normal range (30-80 ng/ml) pending the performance of a randomized controlled clinical trial. Numerous studies of the safety of vitamin D_3 are available (21) that would make such a strategy worth considering.

Acknowledgements

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