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Review

25-Hydroxyvitamin D and Breast Cancer, Colorectal Cancer, and Colorectal Adenomas: Case–Control *versus* Nested Case–Control Studies

WILLIAM B. GRANT

Sunlight, Nutrition, and Health Research Center, San Francisco, CA, U.S.A.

Abstract. *Background: Existing literature includes concerns regarding reliability of case–control studies of breast cancer incidence with respect to 25-hydroxyvitamin D (25(OH)D) concentrations. For breast cancer, only case–control studies consistently find inverse correlations between 25(OH)D and breast cancer. However, for colorectal cancer, nested case–control studies find significant inverse correlations with respect to 25(OH)D concentrations at baseline for mean follow-up times of 7 years. Materials and Methods: This is a review of results currently existing in literature. Results: I provide evidence that 25(OH)D concentration values are only useful for short follow-up times for breast cancer since it develops rapidly. To support the robust nature of breast cancer case–control studies, I show that results from 11 studies from seven countries align in a robust power-law fit to the odds ratio versus mean 25(OH)D concentrations. Conclusion: Case–control studies of breast cancer incidence rates provide reliable results.*

The role of solar ultraviolet-B (UVB) irradiance and vitamin D in reducing breast cancer risk was hypothesized in 1989-90 (1-3). Many ecological, observational, and laboratory studies and randomized controlled trials (RCTs) have since examined solar UVB and vitamin D in reducing breast cancer risk and increasing survival. Ecological studies have found significant inverse correlations between solar UVB indices and incidence and/or mortality rates of breast cancer in Australia, China, France, Nordic countries, Spain, and the United States (4). Case–control studies have found significant inverse correlations between 25-hydroxyvitamin D (25(OH)D) concentrations and breast cancer incidence (5); however, nested case–control studies from cohort studies have not, as discussed in several meta-analyses (6-12). This divergence has given rise to concern that reverse causality might affect case–control studies – *i.e.*, that disease state affects 25(OH)D concentrations. Studies have associated higher 25(OH)D concentrations at diagnosis with improved prognosis (13, 14). The mechanisms whereby vitamin D reduces risk of breast cancer and increases survival are well-known, including effects on cellular differentiation and proliferation, angiogenesis, and metastasis (4). Two RCTs of vitamin D plus calcium support vitamin D's role in reducing breast cancer risk (15, 16). Solar UVB and vitamin D satisfy Hill's criteria for causality in a biological system for breast cancer (17). Yet, since nested case–control studies do not support the UVB–vitamin D–breast cancer hypothesis and since RCTs are considered weak, the scientific community has not widely accepted the role of UVB and vitamin D in reducing cancer risk.

This article explores reasons for the difference between case–control and nested case–control studies of breast cancer incidence with respect to 25(OH)D concentrations.

Correspondence to: William B. Grant, Sunlight, Nutrition, and Health Research Center P.O. Box 641603, San Francisco, CA 94164-1603, U.S.A. Tel: +1 4154091980, e-mail: wbgrant@infionline.net/ www.sunarc.org

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Materials and Methods

The present article updates two earlier studies. One addresses how follow-up time affects incidence of breast and colorectal cancer (18). The other is on the 25(OH)D concentration–breast cancer incidence relation based on case–control studies (5).

Table I gives data for the breast cancer incidence rates used to examine how follow-up time affects relative risk (RR).

The data are primarily for the same studies as in Table II of an earlier paper (18). The RR ratios or odds ratios (ORs) are for a change in 25(OH)D concentration of 50 nmol/L, as calculated in another paper (7), except for two additional studies, for which changes were easy to determine. One study gave the OR for a continuous variation (29). Another gave ORs for five ethnic groups with approximately equal case and control groups (106 to 229) (11), which were then averaged. From the original papers, I either obtained the mean years of follow-up before breast cancer diagnosis

or estimated the value as half the total follow-up period. Some confusion was present in my previous paper (18) regarding whether "follow-up time" meant follow-up time or mean follow-up time before cancer diagnosis.

Table II gives median 25(OH)D concentration quantiles as well as RRs for these values for breast cancer case–control studies.

For colorectal cancer, I obtained RR values for an increase of 50 nmol/L for several studies from a meta-analysis (35). I obtained data from three additional studies from the original papers (36-38). Table III gives the data used.

Data for colorectal adenomas came from Tables I and II in Appendix B of a meta-analysis (7). The case–control studies included those by Levine and colleagues (44), Peters and colleagues (45), Fedirko and colleagues (46), and Takahashi and colleagues (47). The nested case–control studies included those by Platz and colleagues (48), Peters and colleagues (49), and Jacobs and colleagues (50). The data set included one randomized, double-blind, placebo-controlled trial (51) and one cross-sectional study (52).

I used KaleidaGraph 4.02 (Synergy Software, Reading, PA, USA) to graph data for OR *versus* mean 25(OH)D concentration for the quantiles.

Table I. *Data for breast cancer incidence as a function of mean follow-up time to diagnosis.*

Mean follow-up before diagnosis (years)	RR for 50 nmol/L (95% CI)	Reference
0	0.60 (0.47-0.77)	(19)
0	0.43 (0.35-0.54)	(20)
0	0.67 (0.53-0.85)	(21)
0	0.74 (0.61-0.89)	(22)
0	0.45 (0.35-0.56)	(23)
2.7	0.60 (0.54-0.67)	(24)
3.1	0.94 (0.75-1.30)	(12)
3.4	0.85 (0.71-1.01)	(25)
3.5	1.02 (0.82-1.27)	(26)
3.5	0.82 (0.65-1.04)	(27)
3.9	1.05 (0.83-1.33)	(28)
4.0	1.01 (0.86-1.19)	(29)

Results

For both case–control and nested case–control studies, Figure 1 plots RRs with 95% confidence intervals (CIs) for breast cancer incidence for a 50-nmol/L increase in 25(OH)D concentration against years of mean follow-up to diagnosis. The linear regression fit to the RR had the form RR=0.57+0.10 year, r=0.84.

Figure 2 shows OR *versus* mean or median value of 25(OH)D concentration quantiles for breast cancer case–control studies. The data were fit with a power law, $OR=18.5\times[25(OH)D]^{-0.837}$, R=0.90. Rapid change in OR is evident from 15 to 40 nmol/L, a moderate change from 40 to 80 nmol/L, and then little change thereafter. Showing remarkable consistency in their relation, Figure 2 consists of data from 11 studies from seven countries.

Figure 3 plots RRs with 95% CIs for colorectal cancer for a 50-nmol/L increase against years of follow-up. The linear fit to the RR had the form RR=0.45+0.039 year, r=0.34.

Figure 4 shows case–control studies of colorectal adenoma with respect to 25(OH)D concentration. All but one, (49) for men, had an inverse correlation. Figure 5 is the same as Figure 4 except that it is for the nested case–control studies; randomized double-blind, placebo-controlled trial; and cross-sectional studies. Three studies had direct correlations with 25(OH)D: one with 6 years of follow-up (48), one with 1 and 4 years (51), and one with unspecified follow-up (49).

Discussion

This review again shows that case–control studies of 25(OH)D concentration and breast cancer incidence have different outcomes from those of nested case–control studies. I present evidence that the difference occurs because breast cancer develops rapidly, so that within a short period –generally less than the follow-up time of nested case-control studies– the 25(OH)D concentration measured at enrollment loses predictive value. Two earlier papers of mine made this point. Both showed that for breast and colorectal cancer and all-cause mortality rate, the longer the follow-up time, the less likely that a significant finding would exist–and, if so, the OR was reduced (18, 53). In the present study, slopes of RR for cancer incidence with respect to years of follow-up, the ratio for breast cancer to colorectal cancer was 0.10/0.039, or a factor of 2.6 times. This ratio does not translate directly to a difference in tumor growth rates but is probably related to that difference.

A study from Denmark offers evidence that 25(OH)D concentrations can change significantly over moderate intervals at the population level. This article examined the relation between 25(OH)D concentration at enrollment in a cohort study and incidence of cancer (54). Mean serum 25(OH)D levels for like-age populations decreased from 65 nmol/L in 1993-94 to 52 nmol/L in 1999-2001 and 44 nmol/L in 2006-08 (Table II) (54).

At least two reasons exist to consider that breast cancer tumors develop faster than other tumors do, *e.g.* colorectal. For one, breast cancer has a seasonal variation in detection rates, being highest in spring and fall (55). The authors of that study hypothesized that vitamin D production in summer and melatonin production in winter could explain the findings. A second reason is that the American Cancer Society recommends mammographic screening every year for women older than 40 years but only every 5-10 years for colorectal cancer (56).

I consider colorectal adenomas here because they can progress to colorectal cancer (albeit only 5%) (57), which has the strongest evidence for the role of solar UVB and

Table II. *Data for breast cancer case–control studies*.

Reference	Follow-up (years)	Median 25(OH)D concentration for quantiles (nmol/L)	RRs for 25(OH)D concentration for quantiles	Location
(19)	0	25, 76, 128, 154	5.83, 1.83, 1.61, 1.0	UK
(20)	0	23.9, 38, 41.8, 67.4, 88.7	1.0, 0.65, 0.56, 0.49, 0.35	Germany
(21)	0	25.1, 36.0, 51.3, 76.8	1.0, 0.70, 0.66, 0.48	Germany
(22)	0	35.1, 59.8, 86.2, 110.1	1.0, 0.80, 0.83, 0.56	U.S.
(23)	0	37.5, 62.5, 87.5	1.0, 0.81, 0.37	New York, U.S.
(30)	0	41.5, 62.4, 88.3	1.0, 0.54, 0.45	Mexico
(31)	0	38, 64, 98	2.41, 1.52, 1.0	New York, U.S.
(32)	0	18, 40, 60, 85	2.3, 2.5, 2.5, 1.0	Australia
(9)	0	15, 30, 39, 57	3.0, 1.3, 0.72, 0.30	Shanghai
(33)	0	30, 46, 61, 78, 100	3.3, 1.9, 1.7, 2.6, 1.0	U.S.
(34)	0	15, 37, 60	6.5, 4.0, 1.0	Iran

vitamin D in reducing risk (58). The comparison with colorectal adenomas also supports the hypothesis that case–control studies yield useful results. Four out of the five case–control studies showed significant inverse correlations between 25(OH)D concentration, whereas only four of the seven other studies did. The authors of one meta-analysis expressed no concern that their study included four case–control studies, five nested case–control studies, and two cross-sectional studies (59).

A meta-analysis of nested case–control studies separating findings between pre-menopause and post-menopause found no significant correlation for breast cancer risk *versus* 25(OH)D concentration for premenopausal women. But it did find a significantly reduced risk for postmenopausal women with 25(OH)D concentration of 35 ng/mL (RR=0.81 [95% CI=0.69-0.96], p=0.01) and 40 ng/mL (RR=0.83 [95%CI= 0.71-0.97], p=0.02) (8).

Further evidence that vitamin D reduces breast cancer risk comes from ecological studies of breast cancer incidence and/or mortality rate with respect to geographical variation of solar UVB doses. Boscoe and colleagues inversely correlated breast cancer incidence rates with solar UVB doses in the U.S. (60). Ecological studies also inversely correlated with an index of outdoor work in a study of cancer incidence in Nordic countries (61). A study in China found that breast cancer incidence rates directly correlated with solar UVB doses, whereas mortality rates correlated inversely (62). Breast cancer mortality rates inversely correlated with solar UVB doses in Australia (63), China (62), France (64), Japan (65), Spain (66), and the U.S. (3, 60, 67, 68). Many of these studies adjusted findings with respect to other cancer risk–modifying factors. Increasing evidence indicates that vitamin D is more effective at reducing cancer progression than incidence (69, 70).

As to whether solar UVB's only benefit on risk of cancer is through vitamin D production, a recent paper found that other, not yet identified mechanisms exist whereby UV irradiance reduces cancer progression. In a mouse model of intestinal tumor growth, mice with 25(OH)D concentrations raised to 62±31 nmol/L by UVB irradiance (VD^-/UV^+) had significantly fewer adenocarcinomas and lower mean area per tumor than mice with 25(OH)D concentrations raised to 75±15 nmol/L *via* oral vitamin D (VD^+/UV^-) and controls (VD^-/UV^-) with 25(OH)D concentrations of 8 nmol/L (71). However, VD^+/UV^- mice had only slightly lower numbers and areas of adenocarcinomas than VD^-/UV^- mice. This finding suggests that ecological studies of UVB doses and cancer incidence and mortality rates may only partly relate to vitamin D production. The original UVB–vitamin D–cancer hypothesis was based on the assumption that vitamin D production was the most important physiological effect of solar irradiance (72).

One concern regarding the case–control studies is that people with more advanced breast cancer may have lower

Table III. *Data for colorectal cancer as a function of mean follow-up time to diagnosis*.

Mean follow-up before diagnosis (years)	RR for 50 nmol/L (95% CI)	Reference
0.0	0.33 (0.00-0.93)	(36)
1.7	0.60 (0.33-1.07)	(37)
3.9	0.58 (0.41-0.80)	(38)
4.4	0.70 (0.41-1.20)	Health Professionals Follow-up Study (39)
4.5	0.56 (0.24-1.30)	(40)
5.5	0.55 (0.33-0.92)	Nurses' Health Study (41)
5.8	0.69 (0.28-1.68)	Males (42)
5.8	1.21 (0.45-3.27)	Females (42)
7.0	0.37 (0.22-0.63)	(43)

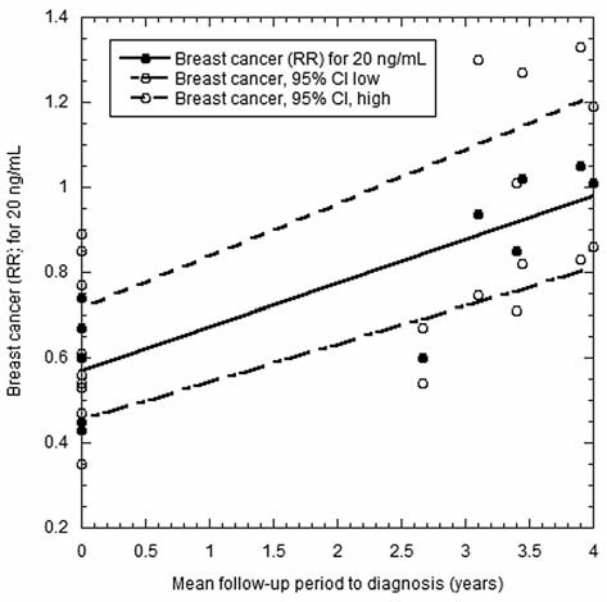

Figure 1. *Plot of RR for breast cancer incidence versus mean follow-up period with linear regression fits.*

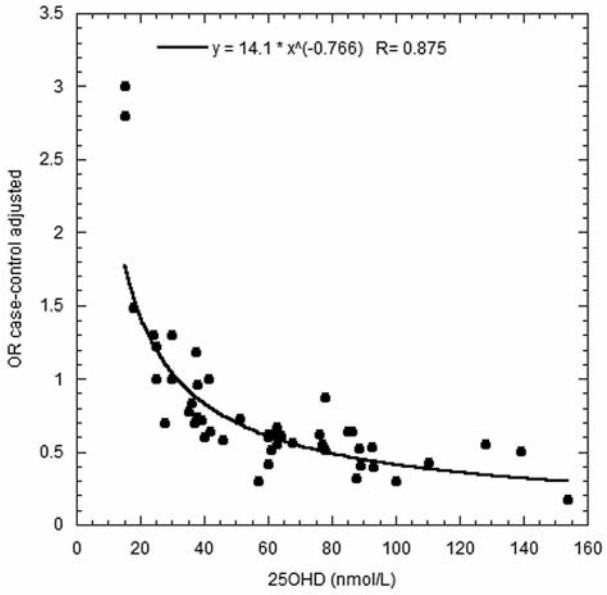

Figure 2. *Plot of OR or RR for breast cancer incidence versus mean 25(OH)D concentration of quantiles for 11 case–control studies from seven countries. Original OR or RR values were multiplied by factors to bring them into agreement along the power-law regression fit.*

25(OH)D concentrations. However, the same findings would seem to be made for nested case–control studies of breast cancer or colorectal cancer as well. Therefore, this concern seems not to affect the difference between breast cancer case–control and nested case–control studies. Another concern is that disease state may affect 25(OH)D concentration (reverse causality). This concern is unlike for certain reasons. One is that women diagnosed with breast cancer are generally unaware of having it until so diagnosed, so they are unlikely to change sun exposure or vitamin D intake habits before diagnosis. Also, little or no evidence exists that breast cancer affects 25(OH)D concentrations per se.

Observational studies of breast cancer mortality rates with respect to 25(OH)D concentrations also support vitamin D's role in reducing breast cancer risk. A meta-analysis of 25(OH)D concentrations at diagnosis found that high *versus* low25(OH)D concentrations were significantly associated with lower breast cancer mortality (pooled RR=0.58 [95% CI=0.40-0.85]) and overall mortality (pooled RR=0.61 [95% CI=0.48-0.79]) (12). Four studies included regarded breast cancer–specific mortality (13, 73-75). The six studies regarding all-cause mortality rate included those four plus Goodwin and colleagues and Jacobs and colleagues (76, 77).

RCTs offer some evidence for a beneficial effect of vitamin D in reducing breast cancer risk. An RCT of postmenopausal women in Nebraska divided subjects into

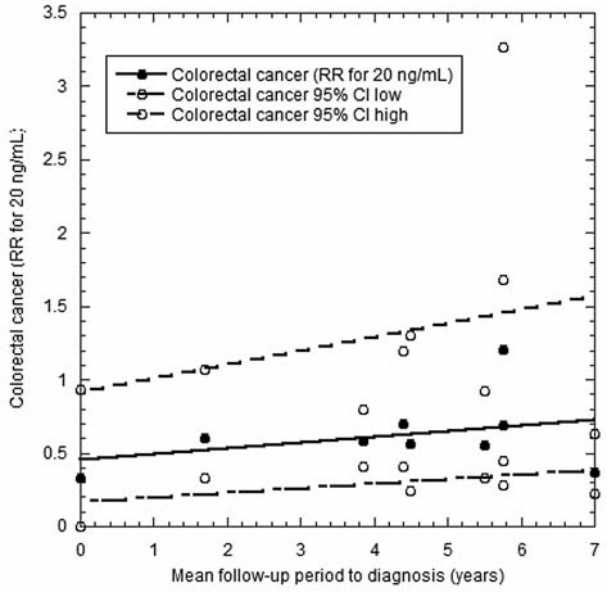

Figure 3. *Plot of RR for colorectal cancer incidence versus mean follow-up period with linear regression fits.*

three arms–placebo, 1,450 mg/d calcium, and 1,450 mg/d calcium plus 1,100 IU/d vitamin D3. Between the ends of the first and fourth years, the RR was 0.23 (95% CI=0.09-0.60; $p<0.005$),whereas that for the calcium-only arm was 0.40 ($p=0.01$) (15). In the Women's Health Initiative study,

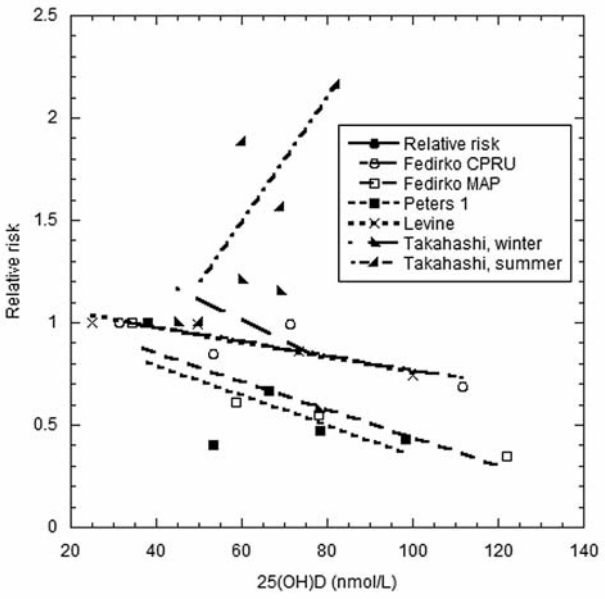

Figure 4. *Plot of ORs for colorectal adenoma versus mean values of 25(OH)D concentrations for quantiles for case–control studies.*

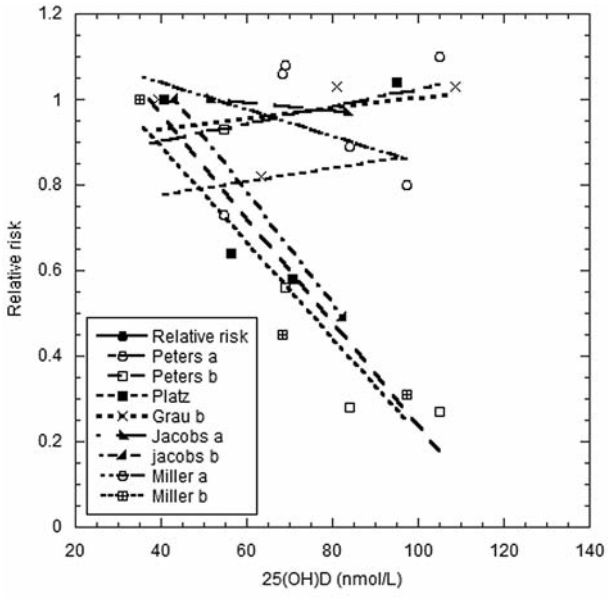

Figure 5. *Same as Figure 4 but for other types of studies.*

"In 15,646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, CaD significantly decreased the risk of total, breast, and invasive breast cancers by 14-20% and nonsignificantly reduced the risk of colorectal cancer by 17%. In women taking personal calcium or vitamin D supplements, CaD did not alter cancer risk (HR=1.06-1.26)" (16).

No other vitamin D RCTs have shown a beneficial effect on cancer rates, although they may have been poorly-designed and conducted. Such RCTs have been largely based on the pharmaceutical model, which assumes that the agent in the trial is the only source of the agent and that a linear dose–response relation exists between agent and health outcome. Neither assumption is valid for vitamin D trials. Robert Heaney recently proposed guidelines for nutritional studies that apply to vitamin D (78): 1. Start with an understanding of the 25(OH)D concentration–health outcome relation. 2. Measure 25(OH)D concentrations of prospective trial participants and include only those with 25(OH)D concentrations near the low- end of the relation. 3. Supplement with enough vitamin D3 to raise 25(OH)D concentrations to near the upper end of the relation. 4. Re-measure 25(OH)D concentrations. 5. Ensure that important cofactors are optimized.

Few vitamin D RCTs followed these guidelines. RCTs that found significant benefits of vitamin D supplementation were more likely to be conducted on people with low 25(OH)D concentrations. Dark skin pigmentation or low solar UVB irradiance (for example, caused by clothing styles or staying indoors when sick) accounted for these low concentrations. Fifty percent of trials conducted on populations with mean baseline 25(OH)D concentrations below 48 nmol/L found beneficial effects on biomarkers of inflammation, while only 20% of those with 25(OH)D concentration above 52 nmol/L, a value typical of many populations, did (Cannell, Grant, and Holick, manuscript in review). The study by Lappe and colleagues (15) is an exception. The re-analysis by Bolland (16) shows the importance of low baseline 25(OH)D concentration for a successful trial.

Conclusion

The evidence and analysis presented herein support the hypothesis that both case–control and nested case–control studies are appropriate for colorectal cancer studies but that only case–control studies of breast cancer accurately and reliably determine the 25(OH)D concentration–breast cancer incidence relation, whereas nested case–control studies with mean follow-up times longer than 3 years prior to diagnosis do not. The reason for the difference is that breast cancer develops much faster than colorectal cancer, so baseline 25(OH)D concentrations lose predictive ability fairly quickly. Thus, breast cancer should join colorectal cancer as significantly reduced by higher 25(OH)D concentrations in addition to greater solar UVB irradiance.

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