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

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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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.

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.

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×[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

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)

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

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)

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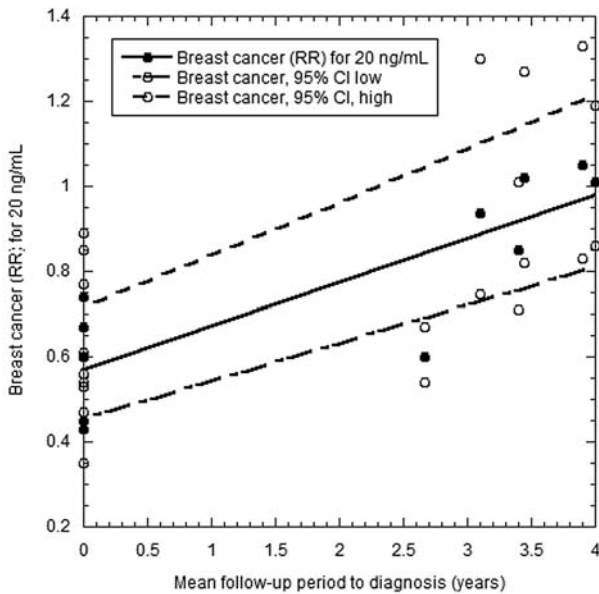
Figure 1. *Plot of RR for breast cancer incidence versus mean follow-up period with linear regression fits.*
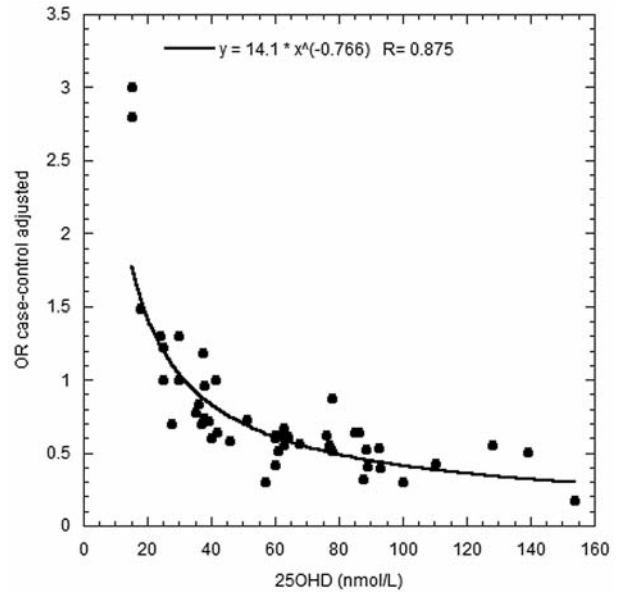

Figure 2. *Plot of OR or RR for breast cancer incidence versus mean 25(OH)D concentration of quantiles for 11 case–control studies from seven countries. Original OR or RR values were multiplied by factors to bring them into agreement along the power-law regression fit.*

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* low 25(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
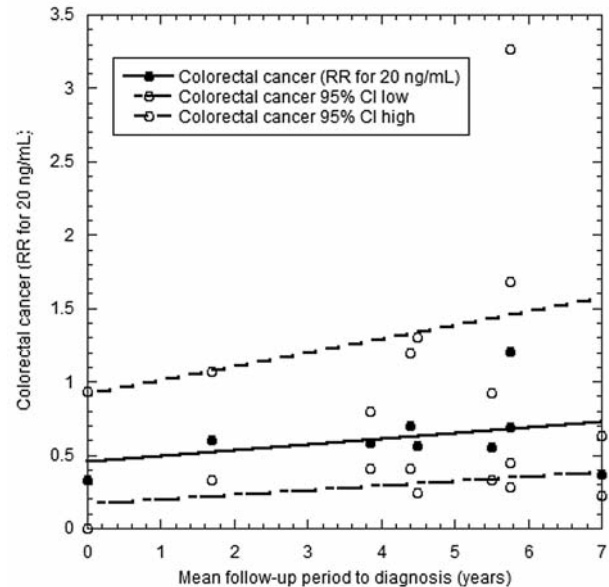

Figure 3. *Plot of RR for colorectal cancer incidence versus mean follow-up period with linear regression fits.*

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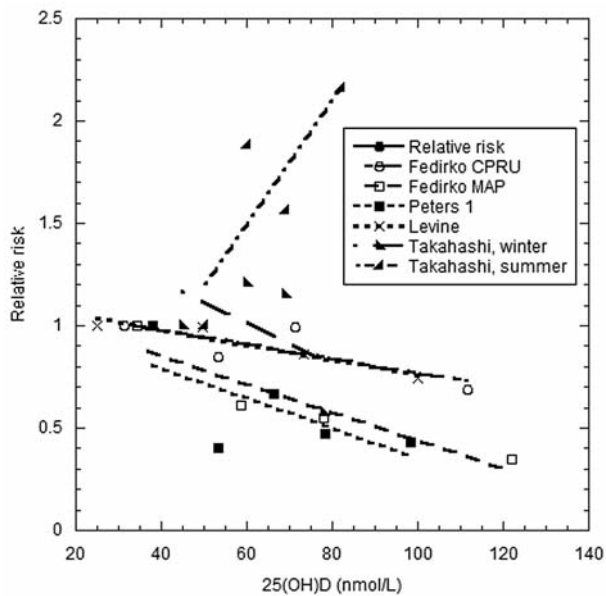
Figure 4. *Plot of ORs for colorectal adenoma versus mean values of 25(OH)D concentrations for quantiles for case–control studies.*
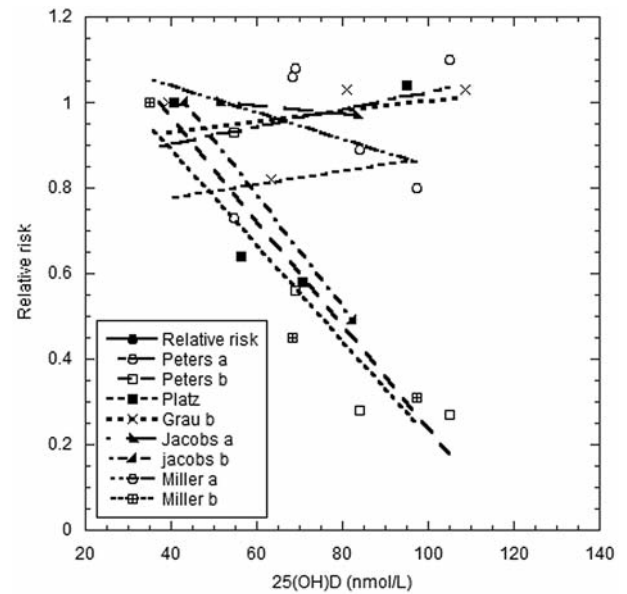

Figure 5. *Same as Figure 4 but for other types of studies.*

"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.

Disclosure

References

1 Colston KW, Berger U and Coombes RC: Possible role for vitamin D in controlling breast cancer cell proliferation. Lancet *1(8631)*: 188-191, 1989.

2 Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK and Gorham ED: Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet *2(8673)*: 1176-1178, 1989.

3 Garland FC, Garland CF, Gorham ED and Young JF: Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med *19(6)*: 614-622, 1990.

4 Moukayed M and Grant WB: Molecular link between vitamin D and cancer prevention. Nutrients *5(10)*: 3993-4021, 2013.

5 Grant WB: The role of animal products and vitamin D in risk of breast cancer. Nutr Clin Pract *28(1)*: 140, 2013.

6 Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, Mullie P and Autier P: Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer *128(6)*: 1414-1424, 2011.

7 Yin L, Grandi N, Raum E, Haug U, Arndt V and Brenner H: Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer *46(12)*: 2196-2205, 2010.

8 Bauer SR, Hankinson SE, Bertone-Johnson ER and Ding EL: Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore) *92(3)*: 123-131, 2013.

9 Chen P, Li M, Gu X, Liu Y, Li X, Li C, Wang Y, Xie D, Wang F, Yu C, Li J, Chen X, Chu R, Zhu J, Ou Z and Wang H: Higher blood 25(OH)D level may reduce the breast cancer risk: evidence from a Chinese population based case-control study and meta-analysis of the observational studies. PLoS One *8(1)*: e49312, 2013.

10 Wang D, Velez de-la-Paz OI, Zhai JX and Liu DW: Serum 25-hydroxyvitamin D and breast cancer risk: a meta-analysis of prospective studies. Tumour Biol *34(6)*: 3509-3517, 2013.

11 Kim Y, Franke AA, Shvetsov YB, Wilkens LR, Cooney RV, Lurie G, Maskarinec G, Hernandez BY, Le Marchand L, Henderson BE, Kolonel LN and Goodman MT: Plasma 25-hydroxyvitamin D_3 is associated with decreased risk of postmenopausal breast cancer in whites: a nested case-control study in the multiethnic cohort study. BMC Cancer *14*: 29, 2014.

12 Kim Y and Je Y: Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer *110(11)*: 2772-2784, 2014.

13 Tretli S, Schwartz GG, Torjesen PA and Robsahm TE: Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. Cancer Causes Control *23(2)*: 363-370, 2012.

14 Toriola AT, Nguyen N, Scheitler-Ring K and Colditz GA: Circulating 25-hydroxyvitamin D levels and prognosis among cancer patients: a systematic review. Cancer Epidemiol Biomarkers Prev *23(6)*: 917-933, 2014.

15 Lappe JM, Travers-Gustafson D, Davies KM, Recker RR and Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr *85(6)*: 1586-1591, 2007.

16 Bolland MJ, Grey A, Gamble GD and Reid IR: Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. Am J Clin Nutr *94(4)*: 1144-1149, 2011.

17 Mohr SB, Gorham ED, Alcaraz JE, Kane CI, Macera CA, Parsons JK, Wingard DL and Garland CF: Does the evidence for an inverse relationship between serum vitamin D status and breast cancer risk satisfy the Hill criteria? Dermatoendocrinol *4(2)*: 152-157, 2012.

18 Grant WB: An estimate of the global reduction in mortality rates through doubling vitamin D levels. Eur J Clin Nutr *65(9)*: 1016-1026, 2011.

19 Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG and Colston KW: Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer *41(8)*: 1164-1169, 2005.

20 Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D and Chang-Claude J: Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer – results of a large case-control study. Carcinogenesis *29(1)*: 93-99, 2008.

21 Abbas S, Chang-Claude J and Linseisen J: Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. Int J Cancer *124(1)*: 250-255, 2009.

22 Crew KD, Shane E, Cremers S, McMahon DJ, Irani D and Hershman DL: High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol *27(13)*: 2151-2156, 2009.

23 Yao S, Sucheston LE, Millen AE, Johnson CS, Trump DL, Nesline MK, Davis W, Hong CC, McCann SE, Hwang H, Kulkarni S, Edge SB, O'Connor TL and Ambrosone CB: Pretreatment serum concentrations of 25-hydroxyvitamin D and breast cancer prognostic characteristics: a case-control and a case-series study. PLoS One *6(2)*: e17251, 2011.

24 Rejnmark L, Tietze A, Vestergaard P, Buhl L, Lehbrink M, Heickendorff L and Mosekilde L: Reduced prediagnostic 25-hydroxyvitamin D levels in women with breast cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev *18(10)*: 2655-2660, 2009.

25 Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC and Hankinson SE: Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev *14(8)*: 1991-1997, 2005.

26 McCullough ML, Stevens VL, Patel R, Jacobs EJ, Bain EB, Horst RL, Gapstur SM, Thun MJ and Calle EE: Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. Breast Cancer Res *11(4)*: R64, 2009.

27 Chlebowski RT: Vitamin D and breast cancer incidence and outcome. Anticancer Agents Med Chem *13(1)*: 98-106, 2013.

28 Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, McCarty CA, Hollis BW, Graubard BI, Berg CD and Ziegler RG: Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev *17(4)*: 889-894, 2008.

29 Kuhn T, Kaaks R, Becker S, Eomois PP, Clavel-Chapelon F, Kvaskoff M, Dossus L, Tjonneland A, Olsen A, Overvad K, Chang-Claude J, Lukanova A, Buijsse B, Boeing H, Trichopoulou A, Lagiou P, Bamia C, Masala G, Krogh V, Sacerdote C, Tumino R, Mattiello A, Buckland G, Sanchez MJ, Menendez V, Chirlaque MD, Barricarte A, Bueno-de-Mesquita HB, van Duijnhoven FJ, van Gils CH, Bakker MF, Weiderpass E, Skeie G, Brustad M, Andersson A, Sund M, Wareham N, Khaw KT, Travis RC, Schmidt JA, Rinaldi S, Romieu I, Gallo V, Murphy N, Riboli E and Linseisen J: Plasma 25-hydroxyvitamin D and the risk of breast cancer in the European prospective investigation into cancer and nutrition: a nested case-control study. Int J Cancer *133(7)*: 1689-1700, 2013.

30 Fedirko V, Torres-Mejia G, Ortega-Olvera C, Biessy C, Angeles-Llerenas A, Lazcano-Ponce E, Saldana-Quiroz VA and Romieu I: Serum 25-hydroxyvitamin D and risk of breast cancer: results of a large population-based case-control study in Mexican women. Cancer Causes Control *23(7)*: 1149-1162, 2012.

31 Peppone LJ, Rickles AS, Janelsins MC, Insalaco MR and Skinner KA: The association between breast cancer prognostic indicators and serum 25-OH vitamin D levels. Ann Surg Oncol *19(8)*: 2590-2599, 2012.

32 Bilinski K and Boyages J: Association between 25-hydroxyvitamin D concentration and breast cancer risk in an Australian population: an observational case-control study. Breast Cancer Res Treat *137(2)*: 599-607, 2013.

33 Mohr SB, Gorham ED, Alcaraz JE, Kane CI, Macera CA, Parsons JK, Wingard DL, Horst R and Garland CF: Serum 25-hydroxyvitamin D and breast cancer in the military: a case-control study utilizing pre-diagnostic serum. Cancer Causes Control *24(3)*: 495-504, 2013.

34 Yousef FM, Jacobs ET, Kang PT, Hakim IA, Going S, Yousef JM, Al-Raddadi RM, Kumosani TA and Thomson CA: Vitamin D status and breast cancer in Saudi Arabian women: case-control study. Am J Clin Nutr *98(1)*: 105-110, 2013.

35 Yin L, Grandi N, Raum E, Haug U, Arndt V and Brenner H: Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Ther *30(2)*: 113-125, 2009.

36 Yaylim-Eraltan I, Arzu Ergen H, Arikan S, Okay E, Ozturk O, Bayrak S and Isbir T: Investigation of the VDR gene polymorphisms association with susceptibility to colorectal cancer. Cell Biochem Funct *25(6)*: 731-737, 2007.

37 Woolcott CG, Wilkens LR, Nomura AM, Horst RL, Goodman MT, Murphy SP, Henderson BE, Kolonel LN and Le Marchand L: Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev *19(1)*: 130-134, 2010.

38 Jenab M, Bueno-de-Mesquita HB, Ferrari P, van Duijnhoven FJ, Norat T, Pischon T, Jansen EH, Slimani N, Byrnes G, Rinaldi S, Tjonneland A, Olsen A, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Kaaks R, Linseisen J, Boeing H, Bergmann MM, Trichopoulou A, Misirli G, Trichopoulos D, Berrino F, Vineis P, Panico S, Palli D, Tumino R, Ros MM, van Gils CH, Peeters PH, Brustad M, Lund E, Tormo MJ, Ardanaz E, Rodriguez L, Sanchez MJ, Dorronsoro M, Gonzalez CA, Hallmans G, Palmqvist R, Roddam A, Key TJ, Khaw KT, Autier P, Hainaut P and Riboli E: Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations:a nested case-control study. BMJ *340*: b5500, 2010.

39 Wu-Wong JR, Nakane M, Ma J, Ruan X and Kroeger PE: VDR-mediated gene expression patterns in resting human coronary artery smooth muscle cells. J Cell Biochem *100(6)*: 1395-1405, 2007.

40 Tangrea J, Helzlsouer K, Pietinen P, Taylor P, Hollis B, Virtamo J and Albanes D: Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control *8(4)*: 615-625, 1997.

41 Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW and Giovannucci EL: Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev *13(9)*: 1502-1508, 2004.

42 Otani T, Iwasaki M, Sasazuki S, Inoue M and Tsugane S: Plasma vitamin D and risk of colorectal cancer: the Japan Public Health Center-Based Prospective Study. Br J Cancer *97(3)*: 446-451, 2007.

43 Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC and Manson JE: Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med *354(7)*: 684-696, 2006.

44 Levine AJ, Harper JM, Ervin CM, Chen YH, Harmon E, Xue S, Lee ER, Frankel HD and Haile RW: Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk. Nutr Cancer. *39(1)*: 35-41, 2001.

45 Peters U, McGlynn KA, Chatterjee N, Gunter E, Garcia-Closas M, Rothman N and Sinha R: Vitamin D, calcium, and vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiol Biomarkers Prev *10(12)*: 1267-1274, 2001.

46 Fedirko V, Bostick RM, Goodman M, Flanders WD and Gross MD: Blood 25-hydroxyvitamin D3 concentrations and incident sporadic colorectal adenoma risk: a pooled case-control study. Am J Epidemiol *172(5)*: 489-500, 2010.

47 Takahashi R, Mizoue T, Otake T, Fukumoto J, Tajima O, Tabata S, Abe H, Ohnaka K and Kono S: Circulating vitamin D and colorectal adenomas in Japanese men. Cancer Sci *101(7)*: 1695-1700, 2010.

48 Platz EA, Hankinson SE, Hollis BW, Colditz GA, Hunter DJ, Speizer FE and Giovannucci E: Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and adenomatous polyps of the distal colorectum. Cancer Epidemiol Biomarkers Prev *9(10)*: 1059-1065, 2000.

49 Peters U, Hayes RB, Chatterjee N, Shao W, Schoen RE, Pinsky P, Hollis BW and McGlynn KA: Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev *13(4)*: 546-552, 2004.

50 Jacobs ET, Alberts DS, Benuzillo J, Hollis BW, Thompson PA and Martinez ME: Serum 25(OH)D levels, dietary intake of vitamin D, and colorectal adenoma recurrence. J Steroid Biochem Mol Biol *103(3-5)*: 752-756, 2007.

51 Grau MV, Baron JA, Sandler RS, Haile RW, Beach ML, Church TR and Heber D: Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J Natl Cancer Inst *95(23)*: 1765-1771, 2003.

52 Silverman EB, Read RW, Boyle CR, Cooper R, Miller WW and McLaughlin RM: Histologic comparison of canine skin biopsies collected using monopolar electrosurgery, CO_2 laser, radiowave radiosurgery, skin biopsy punch, and scalpel. Vet Surg 36(1): 50-56, 2007.

53 Grant WB: Re: "The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women". Am J Epidemiol 176(9): 838, 2012.

54 Skaaby T, Husemoen LL, Thuesen BH, Pisinger C, Jorgensen T, Roswall N, Larsen SC and Linneberg A: Prospective population-based study of the association between serum 25-hydroxyvitamin-D levels and the incidence of specific types of cancer. Cancer Epidemiol Biomarkers Prev 23(7): 1220-1229, 2014.

55 Oh EY, Ansell C, Nawaz H, Yang CH, Wood PA and Hrushesky WJ: Global breast cancer seasonality. Breast Cancer Res Treat 123(1): 233-243, 2010.

56 McAulay KA, Higgins CD, Macsween KF, Lake A, Jarrett RF, Robertson FL, Williams H and Crawford DH: HLA class I polymorphisms are associated with development of infectious mononucleosis upon primary EBV infection. J Clin Invest 117(10): 3042-3048, 2007.

57 Carvalho B, Sillars-Hardebol AH, Postma C, Mongera S, Terhaar Sive Droste J, Obulkasim A, van de Wiel M, van Criekinge W, Ylstra B, Fijneman RJ and Meijer GA: Colorectal adenoma to carcinoma progression is accompanied by changes in gene expression associated with ageing, chromosomal instability, and fatty acid metabolism. Cell Oncol (Dordr) 35(1): 53-63, 2012.

58 Giovannucci E: Epidemiology of vitamin D and colorectal cancer. Anticancer Agents Med Chem 13(1): 11-19, 2013.

59 Wei MY, Garland CF, Gorham ED, Mohr SB and Giovannucci E: Vitamin D and prevention of colorectal adenoma: a meta-analysis. Cancer Epidemiol Biomarkers Prev 17(11): 2958-2969, 2008.

60 Boscoe FP and Schymura MJ: Solar ultraviolet-B exposure and cancer incidence and mortality in the United States, 1993-2002. BMC Cancer 6: 264, 2006.

61 Grant WB: Role of solar UVB irradiance and smoking in cancer as inferred from cancer incidence rates by occupation in Nordic countries. Dermatoendocrinol 4(2): 203-211, 2012.

62 Chen W, Clements M, Rahman B, Zhang S, Qiao Y and Armstrong BK: Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. Cancer Causes Control 21(10): 1701-1709, 2010.

63 Astbury A. Cancer mortality, cosmic ray neutron dose, and summer solar UV-B flux share similar geographical distributions in the USA.Triumf report TRI-PP-05-24. June 2005

64 Grant WB: Ecological studies of the UVB-vitamin D-cancer hypothesis. Anticancer Res 32(1): 223-236, 2012.

65 Mizoue T: Ecological study of solar radiation and cancer mortality in Japan. Health Phys 87(5): 532-538, 2004.

66 Grant WB and Boucher BJ: Are Hill's criteria for causality satisfied for vitamin D and periodontal disease? Dermatoendocrinol 2(1): 30-36, 2010.

67 Grant WB: An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. Cancer 94(6): 1867-1875, 2002.

68 Grant WB and Garland CF: The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res 26(4A): 2687-2699, 2006.

69 Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, Feldman BS, Pan A, Johnson L, Crowe F, Hu FB and Franco OH: Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ 348: g1903, 2014.

70 Grant WB and Garland CF: Vitamin D has a greater impact on cancer mortality rates than on cancer incidence rates. BMJ 348: g2862, 2014.

71 Rebel H, der Spek CD, Salvatori D, van Leeuwen JP, Robanus-Maandag EC and de Gruijl FR: UV exposure inhibits intestinal tumor growth and progression to malignancy in intestine-specific Apc mutant mice kept on low vitamin D diet. Int J Cancer, 2014.

72 Garland CF and Garland FC: Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 9(3): 227-231, 1980.

73 Hatse S, Lambrechts D, Verstuyf A, Smeets A, Brouwers B, Vandorpe T, Brouckaert O, Peuteman G, Laenen A, Verlinden L, Kriebitzsch C, Dieudonne AS, Paridaens R, Neven P, Christiaens MR, Bouillon R and Wildiers H: Vitamin D status at breast cancer diagnosis: correlation with tumor characteristics, disease outcome, and genetic determinants of vitamin D insufficiency. Carcinogenesis 33(7): 1319-1326, 2012.

74 Villasenor A, Ballard-Barbash R, Ambs A, Bernstein L, Baumgartner K, Baumgartner R, Ulrich CM, Hollis BW, McTiernan A and Neuhouser ML: Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. Cancer Causes Control 24(4): 759-767, 2013.

75 Vrieling A, Seibold P, Johnson TS, Heinz J, Obi N, Kaaks R, Flesch-Janys D and Chang-Claude J: Circulating 25-hydroxyvitamin D and postmenopausal breast cancer survival: Influence of tumor characteristics and lifestyle factors? Int J Cancer 134(12): 2972-2983, 2014.

76 Goodwin PJ, Ennis M, Pritchard KI, Koo J and Hood N: Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. J Clin Oncol 27(23): 3757-3763, 2009.

77 Jacobs ET, Thomson CA, Flatt SW, Al-Delaimy WK, Hibler EA, Jones LA, Leroy EC, Newman VA, Parker BA, Rock CL and Pierce JP: Vitamin D and breast cancer recurrence in the Women's Healthy Eating and Living (WHEL) Study. Am J Clin Nutr 93(1): 108-117, 2011.

78 Heaney RP: Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutr Rev 72(1): 48-54, 2014.