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Vitamin D and Breast Cancer

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Though the relationship between vitamin D and breast cancer remains unclear, a growing body of evidence suggests that vitamin D may modestly reduce risk. A large number of in vitro studies indicate that vitamin D can inhibit cell proliferation and promote apoptosis and cell differentiation in breast tumor tissue. Results from analytic studies of sunlight exposure and dietary intake have been inconsistent but together generally support a modestly protective role of vitamin D, at least in some population subgroups. Studies using blood vitamin D metabolites to assess vitamin D status may be less prone to misclassification than those of diet and sunlight exposure. Overall, the two prospective and four case-control studies of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D tend to support a protective effect in older women. The relationship between common vitamin D receptor polymorphisms and risk remains unclear. Many questions about this relationship clearly remain, including the utility of assessing vitamin D through diet and sunlight exposure, the relationship between plasma metabolites, and the potential modifying effects of age, menopausal status and tumor characteristics. Given that vitamin D status is modifiable, additional prospective studies are necessary to determine if vitamin D may have important potential for breast cancer prevention.
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INTRODUCTION

Although the relationship between vitamin D and breast cancer remains unclear, a growing body of evidence suggests that vitamin D may modestly reduce risk. Both diet and sunlight contribute to circulating vitamin D levels. Dietary intake of fortified dairy foods and cereals, some types of fish, multivitamins, and calcium/vitamin D supplements are significant sources of vitamin D in elderly populations and those with low ambient sunlight exposure (1–3). In populations with ample sun exposure, cutaneous conversion of 7-dehydrocholesterol after solar UVB radiation provides the greater source. Previtamin D from both diet and sunlight sources is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D). 25(OH)D is then further hydroxylated to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by 1α-hydroxylase enzymes; much of this hydroxylation takes place in the kidney nephrons, though recent studies indicate that the breast and other target tissues possess 1α-hydroxylase as well and that some proportion of $1,25(OH)_2D$ is produced and used locally and may never enter systemic circulation (4–8). $1,25(OH)_2D$ is the biologically active metabolite that binds to nuclear vitamin D receptors (VDR) in the intestine, bone, breast, and other tissues (9). A large number of in vitro studies indicate that $1,25(OH)_2D$ can inhibit cell proliferation and promote apoptosis and cell differentiation in breast tumor tissue (5, 10–12), providing a biologic basis for epidemiologic study of this relationship.

Studies of sunlight exposure and dietary vitamin D intake

Early epidemiologic studies of the breast cancer–vitamin D relationship were primarily ecologic. Results from analyses in the United States, Russia, and Canada have shown strong inverse correlations between sunlight exposure and breast cancer incidence and/or mortality rates (13–16). In particular, a study by Garland et al. (13) of 87 U.S. counties reported strong correlations between ambient sunlight and mortality, with the strongest results observed in white women living in urban areas ($r = -0.80$; $p = 0.0001$). In addition, three recent European studies have found significantly longer survival after breast cancer diagnosis in women diagnosed in summer and fall than at other times of the year, perhaps in part due to higher vitamin D availability (17–19).

In the National Health and Nutrition Examination Survey cohort, high sun exposure was associated with a significant lower risk of breast cancer over an average of 17.3 years of follow-up (20). Women self-reporting frequent recreational exposure at baseline had a relative risk (RR) of 0.66 (95% confidence interval [CI] = 0.44 – 0.99; p for trend = 0.08) compared to those reporting exposure never or rarely. Results for occupational sun exposure were similar,

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Selected Abbreviations and Acronyms

UV = ultraviolet radiation
25(OH)D = 25-hydroxyvitamin D
$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D
VDR = vitamin D receptor
NHS = Nurses' Health Study
CPS II = Cancer Prevention Study II
RR = relative risk
OR = odds ratio
CI = confidence interval
ER = estrogen receptor
PR = progesterone receptor

though those for geographic region of residence and exposure as assessed by a physician were less strong.

Results from primary analyses of vitamin D intake and breast cancer risk in three large cohort studies (20–22) and three case-control studies (23–25) were essentially null. In both the Nurses' Health Study (NHS) cohort (21) and the Cancer Prevention Study II (CPS II) Nutrition cohort (22), a slight benefit was observed for women reporting high vitamin D intake from food sources only, but not for total vitamin D (i.e., from foods and supplements) (Fig. 1). For example, over 9 years of follow-up in the CPS II Nutrition cohort, McCullough et al. (22) found that women with

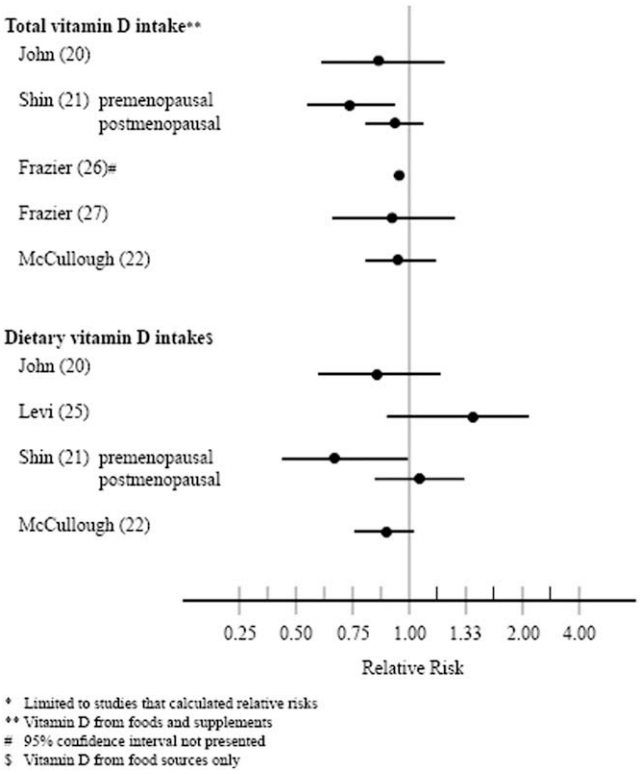

FIGURE 1. Multivariate relative risk and 95% confidence intervals of breast cancer in the highest vs. the lowest category of total vitamin D intake and dietary vitamin D intake*

total vitamin D intake of 700 IU or more at baseline had essentially the same risk as those consuming ⩽100 IU per day (RR = 0.95; 95% CI = 0.81–1.13; *p* for trend = 0.98) (22). In contrast, vitamin D from food sources only was modestly related to cancer incidence but not statistically significant (RR for >300 vs. ⩽100 IU per day = 0.89; 95% CI = 0.76–1.03; *p* for trend = 0.21); the effect of dietary vitamin D was modified by sunlight exposure, with a significant protective effect confined to women living in states with low UV index (*p* for interaction = 0.05). Two additional cohort studies retrospectively assessing adolescent diet did not suggest that vitamin D intake during high school years was related to breast cancer risk later in life (26,27).

In several studies, secondary analyses limited to populations subsets suggest the possibility that the vitamin D–breast cancer relationship may be modified by other factors, such as menopausal status (21) and tumor characteristics (22). In the NHS cohort, Shin and colleagues (21) found that vitamin D intake of 500 IU or more per day was associated with a significant 28% lower risk of breast cancer in premenopausal women (RR = 0.72; 95% CI = 0.55–0.94; *p* for trend = 0.01), though results in postmenopausal women were null (RR = 0.94; 95% CI = 0.80–1.10; p for trend = 0.27) (see Fig. 1). Dietary intake of at least 300 IU per day was associated with a significant lower risk of estrogen receptor (ER)–positive breast cancer in the CPS II Nutrition cohort (RR = 0.74; 95% CI = 0.59–0.93; *p* for trend = 0.006), but not of ER-negative disease (RR = 1.35; 95% CI = 0.79–2.33; *p* trend = 0.82) (22) (Fig. 2).

Studies of Blood Levels of Vitamin D Metabolites

Because multiple sources contribute to circulating vitamin D levels, studies using vitamin D metabolites measurable in whole blood, plasma, or serum to assess vitamin D status may be less prone to misclassification than those relying only on self-report of diet and sunlight exposure. To date, two prospective studies have evaluated how vitamin D metabolites may relate to breast cancer (28,29) (Fig. 3). In a study of Kaiser Permanente Medical Care Program members, Hiatt and colleagues (29) evaluated $1,25(OH)_2D$ levels in 96 matched case-control pairs. Blood samples were collected between 1964 and 1972, and study participants were followed up for an average of 15.4 years for breast cancer development. In multivariable analyses, high serum $1,25(OH)_2D$ levels were not associated with the development of breast cancer (odds ratio [OR] for quartile 4 vs. quartile 1 = 1.0; 95% CI = 0.2–3.4). In contrast, Bertone-Johnson and colleagues (28) reported that high plasma 25(OH)D levels modestly reduced risk of breast cancer in the NHS cohort (RR for quintile 5 vs. quintile 1 = 0.73; 95% CI = 0.49–1.07; *p* for trend = 0.06). The RR for $1,25(OH)_2D$ levels was

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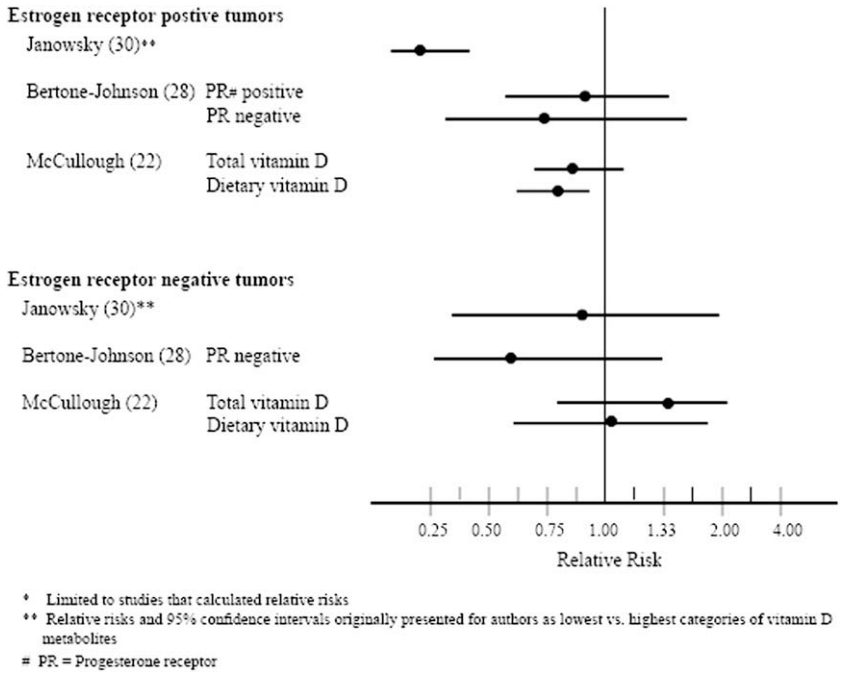
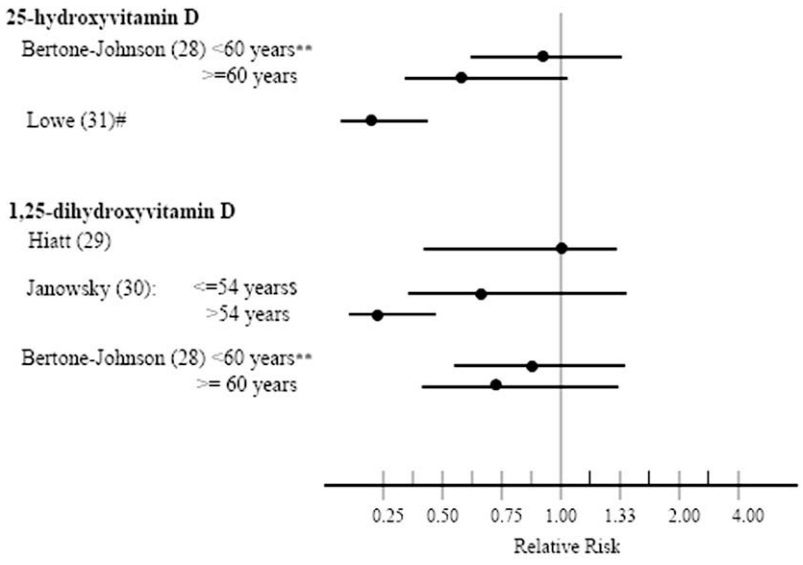


* Limited to studies that calculated relative risks
** Relative risks and 95% confidence intervals originally presented for authors as lowest vs. highest categories of vitamin D metabolites
# PR = Progesterone receptor

FIGURE 2. Multivariable relative risks and 95% confidence intervals of estrogen receptor–positive and estrogen receptor–negative breast cancer in the highest vs. the lowest category of vitamin D.*



* Limited to studies that calculated relative risks
** Age at blood collection
# Relative risks and 95% confidence intervals originally presented by authors for lowest vs. highest categories of vitamin D metabolites
$ Age at breast cancer diagnosis

FIGURE 3. Multivariable relative risks and 95% confidence intervals of breast cancer in the highest vs. the lowest category of blood levels in vitamin D metabolites.*

similar (RR for quintile 5 vs. quintile 1 = 0.76; 95% CI = 0.52–1.11; p for trend = 0.39), though also not statistically significant.

Results from four case-control studies of vitamin D metabolites measured after cancer diagnosis are also inconsistent (30–33). In a study of 156 cases and 184 matched controls, Janowsky and colleagues (30) observed a significant three-fold increase in breast cancer risk in women in the lowest quartile of $1,25(OH)_2D$ from whole blood (OR = 3.2; 95% CI = 1.7–6.0; p for trend <0.001), but no effect of 25(OH)D levels on risk (Fig. 3). In a Brazilian population, serum $1,25(OH)_2D$ levels were significantly lower in breast cancer cases compared to healthy controls ($p = 0.01$), whereas no difference in mean 25(OH)D levels was observed ($p = 0.72$) (32). In contrast, low 25(OH)D was associated with a significant 5-fold increase in risk in one recent study in the United Kingdom (OR for quartile 1 vs. quartile 4 = 5.83; 95% CI = 2.31–14.7) (31). In a second UK study, 25(OH)D levels were significantly lower in breast cancer cases with advanced disease compared with those with early-stage disease (33).

The relationship between the two important vitamin D metabolites and the development of breast cancer thus remains unclear. Correlations between 25(OH)D and $1,25(OH)_2D$ tend to be low (e.g., $r = 0.02$–0.31) (28, 30, 32). While it is $1,25(OH)_2D$ that binds to VDR in target tissues, its production is tightly regulated to maintain calcium homeostatis (9); 25(OH)D is more sensitive to dietary intake and UV exposure and better reflects overall vitamin D status (1, 2, 9). In addition, $1,25(OH)_2D$ metabolized by 1α-hydroxylase in breast tissue may not enter the general circulation and thus may not be measurable by standard plasma assay (5); if the amount of $1,25(OH)_2D$ produced locally is substantial, 25(OH)D measurement may better reflect the total amount of vitamin D ultimately available to breast cells.

Vitamin D Receptor Polymorphisms and Breast Cancer Risk

At least 25 polymorphisms of the VDR gene have been identified, many of which occur at high frequency in Caucasian populations and may influence receptor affinity, binding to nuclear DNA, RNA transcription, and protein synthesis (34). The presence of an *f* allele at *Fok1* leads to the production of a protein that is 3 amino acids longer than that produced by the *F* allele. Several in vitro studies suggest that the longer protein (*f* allele) is a less active transcriptional activator than the shorter protein and is consequently associated with lower VDR activity. The *f* allele was associated with a higher risk of breast cancer in one study (35) but not in others (36–39). Several polymorphisms at the 3′ end of the VDR gene, including *Bsm1*, *Taq1*, and *Apa1*, occur in strong linkage disequilibrium and are linked with a poly(A) microsatellite repeat. Results from in vitro evaluations suggest that together these polymorphisms and the poly(A) are involved in the regulation of gene expression and messenger RNA (mRNA) stability (40). Guy and colleagues (36) reported an increased risk of breast cancer in women with the *bb* genotype of *Bsm1* (OR for *bb* vs. *BB* = 1.92; 95% CI = 1.2–3.1). This finding has been reproduced in some studies in Caucasian, Latina, and Asian populations (31, 37, 41, 42), but not in others (35, 38, 43, 44). *Apa1* has been associated with risk in some studies (39, 42) but not in others (38). Results from the few studies of *Taq1* have largely been null (38, 42, 43, 45–47). Significant increases in risk in women with the LL genotype of the poly(A) have been reported by some investigators (36, 37, 41), but no association was observed by McCullough et al. (38).

Relatively few studies have assessed potential interaction between either vitamin D intake (38) or plasma metabolite levels (31, 35) and VDR polymorphisms, with mixed results. In a study of 179 white breast cancer cases and 131 controls, Lowe and colleagues (31) reported a two-fold increase in risk associated with the *bb* genotype of *Bsm1* (OR for *bb* vs. *BB* = 2.02; 95% CI = 1.03–3.97). Risk was highest for women with low 25(OH)D levels and *bb* genotype (OR vs. high 25(OH)D and *BB*/*Bb* = 6.82; 95% CI = 2.57–17.10). In contrast, McCullough and colleagues (38) did not observe any interaction between vitamin D intake and any of the eight polymorphisms evaluated, though there was some evidence of interaction with calcium intake. The majority of studies of VDR polymorphisms and breast cancer risk have been in Caucasian populations with relatively similar allele frequencies, but it is possible that small population differences may, to some extent, explain the observed inconsistencies. Additional studies evaluating the relationship between VDR polymorphisms and vitamin D metabolite levels are needed for their relationship to breast cancer to be fully understood.

Essential Areas for Future Research

It remains unknown when is the most appropriate time to assess vitamin D status with respect to breast cancer onset. In prospective studies, biochemical, sunlight, and dietary assessments of vitamin D made many years before diagnosis may not reflect levels that are etiologically relevant to the development of the disease. In case-control studies, the presence of a tumor may affect circulating vitamin D levels, either by altering 25(OH)D metabolism (5) or by altering a patient's dietary intake of vitamin D or sunlight exposure. Differences in the timing of measurement may explain some of the inconsistency in study findings. Stronger and/or significant protective effects have been most often observed in studies assessing vitamin D status within a few years of

diagnosis (28, 30–32), while results from prospective studies with longer follow-up periods after vitamin D measurement have generally been less strong (20, 22, 26, 27, 29). It is unclear whether this difference reflects less misclassification of vitamin D status in studies with a short interval between measurement and cancer diagnosis or suggests a short-term etiologic effect of vitamin D on tumor development. Additional prospective studies exploring the timing of vitamin D assessment are clearly warranted.

Several studies suggest that the effect of vitamin D on breast cancer may be modified by other factors. The likelihood of vitamin D deficiency increases with age, due to decreases in cutaneous vitamin D production (8). Estrogen deficiency also appears to reduce vitamin D activation and VDR expression, suggesting that older and postmenopausal women may be at increased risk (5, 48, 49). Most studies have not directly evaluated the role of age and/or estrogen deficiency, though two investigations observed stronger relationships between vitamin D and breast cancer risk in older women (28, 30) (Figs. 1 and 3). In addition, few studies have evaluated how vitamin D may relate to breast cancer risk in non-Caucasian populations (30, 32). Janowsky et al. found that lower $1,25(OH)_2D$ levels associated with a two-fold increase in breast cancer in white women, but not related to risk in black women (OR for below median level vs. above in white women = 2.2; 95% CI = 1.4–3.4; OR for black women = 1.0; 95% CI = 0.4–2.7; p for interaction = 0.15) (30). 25(OH)D levels were lower in black cases than controls, but higher in white cases than controls. Finally, some laboratory evidence suggests that ER-positive cell lines may be more sensitive to the growth regulatory effects of $1,25(OH)_2D$ than ER-negative tumors (5). Other in vitro studies suggest that the action of $1,25(OH)_2D$ on breast tumors may be through pathways other than the disruption of estrogen signaling and that cells derived from ER-negative tumors may undergo regression through apoptosis after exposure to $1,25(OH)_2D$ (50). Whereas some studies have found a relationship between dietary vitamin D intake (22) or metabolite levels (30) only in ER-positive tumors, others have observed stronger protection for ER-negative tumors (28) (see Fig. 2). Additional studies in diverse populations are needed to determine if the vitamin D–breast cancer relationship varies by age, ethnicity, and tumor characteristics.

CONCLUSION

At this time, much about the relationship between vitamin D and breast cancer remains unknown. Relatively few epidemiologic studies have addressed the association, and only a handful of these have been prospective, used biochemical measurements of vitamin D, or been large enough to permit analyses stratified by other factors. Despite many inconsistencies, the potential exists that vitamin D may modestly reduce the risk of breast cancer. Many questions clearly remain, including those concerning the utility of assessing vitamin D through diet and sunlight exposure, the most appropriate timing of assessment, the relationship between the two important plasma metabolites, and potential modifying effects of factors such as age, menopausal status, and tumor characteristics. Given that vitamin D status is fairly easily modifiable through increased sunlight exposure and/or dietary modification, further study is necessary to determine if vitamin D may have important potential for breast cancer prevention.

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