Prospective Studies of Dietary Vitamin D and Breast Cancer: More Questions Raised than Answered

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Prospective studies suggest that dietary vitamin D may at least modestly reduce the risk of breast cancer. This review addresses issues raised by recent studies, including differences in findings related to dietary source of vitamin D, menopausal status, and tumor characteristics. It also discusses the optimal timing of vitamin D assessment.

Key words: breast cancer, vitamin D, diet

INTRODUCTION

Interest in the potentially protective role of vitamin D in cancer development has been increasing steadily over the past decade. A growing body of evidence suggests that vitamin D may protect against some forms of cancer, including breast cancer, in addition to reducing the risk of rickets and bone fracture. Results from recent studies have been encouraging enough to ignite an active debate on whether the current recommendations for vitamin D intake (200 – 600 IU for individuals ≥19 years) are too low and whether the safe tolerable upper intake level (2000 IU per day) should also be revised upwards.1,2

Though subcutaneous conversion of 7-dehydrocholesterol into vitamin D₃ after exposure to solar ultraviolet (UV) B radiation is the source of a substantial proportion of circulating vitamin D in the body, dietary intake is the major source in elderly populations and in those with limited ambient sunlight exposure.3-5 Vitamin D is present in a limited variety of foods, including fortified dairy products, orange juice and cereals, and fatty fish, such as salmon and bluefish. Supplemenal vitamin D, which is often taken along with calcium, is also an important source of dietary vitamin D in many populations. There are two forms of vitamin D, both of which may be present in food sources. Vitamin D₃ (i.e., cholecalciferol) is the product of cholesterol conversion in the skin and also occurs naturally in fish. Vitamin D₂ (i.e., ergocalciferol) is synthesized in the laboratory from plants. Both forms are currently used in food fortification and in multivitamin supplements.6

Vitamin D from sunlight and dietary sources, in both D₂ and D₃ forms, is hydroxylated in the liver to 25-hydroxyvitamin D (25OHD). 25OHD is then further hydroxylated to 1,25-dihydroxyvitamin D (1,25(OH)₂D) by 1alpha-hydroxylase enzymes. Much of this hydroxylation takes place in kidney nephrons, though recent studies indicate that the breast and other target tissues possess 1alpha-hydroxylase and 1,25(OH)₂D is produced locally in these tissues.7 1,25(OH)₂D is the biologically active metabolite that binds to nuclear vitamin D receptors in the intestine, bone, breast, and other tissues.

VITAMIN D AND BREAST CANCER PREVENTION

Despite many decades of research into modifiable risk factors for breast cancer, its incidence remains high. After non-melanoma skin cancers, breast cancer is the most commonly diagnosed malignancy in women in the United States.8 The American Cancer Society estimates that 178,480 cases will be diagnosed in 2007. Mortality from the disease also remains high, with 40,460 deaths expected in 2007. It is essential to continue to evaluate and identify ways for women to reduce their risk of the disease.

Data from a variety of sources provide a biologic rationale for dietary vitamin D intake in breast cancer prevention. 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.7,9,10 Synthetic vitamin D analogues are currently...
being evaluated for their potential use in breast cancer treatment. In early epidemiologic studies, strong correlations between ambient sunlight exposure and breast cancer mortality were observed in ecologic studies in the United States, Canada, and Russia, which further suggested the possibility of an etiologic relationship.\textsuperscript{12-15}

The relationship between dietary vitamin D intake and the risk of breast cancer has been assessed directly in at least five case-control studies, with largely null results.\textsuperscript{16-20} However, case-control studies of diet have substantial methodologic limitations, including the potential for recall and selection biases. Misclassification of dietary information is also common because participants may be asked to remember food intake that occurred many years before the cancer diagnosis. For these reasons, prospective cohort studies are generally better for assessing diet-disease relationships. In these studies, vitamin D intake is assessed in a large population of cancer-free women who are then observed over time for the development of breast cancer. Because vitamin D status is assessed before cancer is diagnosed, prospective studies are generally less susceptible to the common biases in case-control studies. The longitudinal design also permits investigators to evaluate the time period during a woman’s life in which vitamin D may be most important for breast cancer prevention.

**PROSPECTIVE STUDIES OF VITAMIN D AND BREAST CANCER**

With the recent publication of two large prospective studies,\textsuperscript{21,22} combined with three previous evaluations,\textsuperscript{23-25} a substantial body of prospective evidence now exists concerning the relationship between dietary vitamin D and breast cancer (Table 1). In each of these studies, one aspect or more of vitamin D intake was related to breast cancer risk, though results varied, sometimes dramatically, concerning the source of vitamin D most strongly associated with cancer and the characteristics of women receiving the greatest benefit.

The first prospective study to evaluate this relationship was the National Health and Nutrition Examination Survey (NHANES).\textsuperscript{23} Vitamin D obtained from foods and supplements together was weakly and non-signifi-

### Table 1. Major results from prospective studies of dietary vitamin D intake and incidence of breast cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Study duration</th>
<th>No. of cases</th>
<th>Total vitamin D</th>
<th>Vitamin D from food sources</th>
<th>Vitamin D from supplements</th>
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</thead>
<tbody>
<tr>
<td><strong>Premenopausal and postmenopausal women combined</strong></td>
<td></td>
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<td></td>
<td>Daily vs. never</td>
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<tr>
<td>John et al. (1999)\textsuperscript{23}</td>
<td>National Health and Nutrition Examination Survey</td>
<td>1971–1975 through 1992</td>
<td>177</td>
<td>≥200 vs. &lt;100 IU; ≥200 vs. &lt;100 IU; 0.86 (0.61–1.20)</td>
<td>0.85 (0.59–1.24)</td>
<td>0.89 (0.60–1.32)</td>
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<td><strong>Postmenopausal women</strong></td>
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<tr>
<td>Shin et al. (2002)\textsuperscript{24}</td>
<td>Nurses Health Study</td>
<td>1980 through 1996</td>
<td>2345</td>
<td>&gt;500 vs. ≤150 IU; &gt;300 vs. ≤75 IU; 0.94 (0.80–1.10)</td>
<td>1.06 (0.85–1.34)</td>
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<tr>
<td>McCullough et al. (2005)\textsuperscript{25}</td>
<td>CPS II Nutrition Cohort Study</td>
<td>1992–1993 through 2001</td>
<td>2855</td>
<td>&gt;700 vs. ≤100 IU; &gt;300 vs. ≤100 IU; 0.95 (0.81–1.13)</td>
<td>0.89 (0.76–1.03)</td>
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<tr>
<td>Lin et al. (2007)\textsuperscript{21}</td>
<td>Women’s Health Study</td>
<td>1993–1995 through 2004</td>
<td>743</td>
<td>≥548 vs. &lt;162 IU; ≥319 vs. &lt;142 IU; 1.30 (0.97–1.73)</td>
<td>1.22 (0.95–1.55)</td>
<td>≥400 IU vs. none; 0.87 (0.68–1.12)</td>
</tr>
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<td>Robien et al. (2007)\textsuperscript{22}</td>
<td>Iowa Women’s Health Study</td>
<td>1986 through 2004</td>
<td>2440</td>
<td>≥800 vs. &lt;400 IU; ≥800 vs. &lt;400 IU; 0.89 (0.77–1.03)</td>
<td>0.55 (0.24–1.22)</td>
<td>≥800 IU vs. none; 0.89 (0.74–1.08)</td>
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<tr>
<td><strong>Premenopausal women</strong></td>
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<tr>
<td>Shin et al. (2002)\textsuperscript{24}</td>
<td>Nurses Health Study</td>
<td>1980 through 1996</td>
<td>827</td>
<td>&gt;500 vs. ≤150 IU; &gt;300 vs. ≤75 IU; 0.72 (0.55–0.94)</td>
<td>0.66 (0.43–1.00)</td>
<td></td>
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<tr>
<td>Lin et al. (2007)\textsuperscript{21}</td>
<td>Women’s Health Study</td>
<td>1993–1995 through 2004</td>
<td>276</td>
<td>≥548 vs. &lt;162 IU; ≥319 vs. &lt;142 IU; 0.65 (0.42–1.00)</td>
<td>1.02 (0.69–1.53)</td>
<td>≥400 IU vs. none; 0.76 (0.50–1.17)</td>
</tr>
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Abbreviations: MV RR, multivariable relative risk
*Values expressed in international units (IU) per day. Values in parentheses are 95% confidence intervals.
cantly related to breast cancer risk in this population of premenopausal and postmenopausal women. The relative risk (RR) for women consuming ≥200 versus <100 IU per day was 0.86 [95% confidence interval (95%CI) = 0.61–1.20; \( P \) for trend = 0.37]. When evaluated separately, the results for vitamin D from food sources and supplements were virtually identical.

The four studies relating vitamin D intake specifically to postmenopausal breast cancer were remarkably consistent in their results. Regardless of the intake level considered, total vitamin D intake was only minimally related to risk, if at all.\(^ {21,22,24,25} \) For example, in the Cancer Prevention Study (CPS) II Nutrition Cohort, women consuming >700 IU per day had essentially the same incidence of breast cancer as those consuming ≤100 IU per day (RR, 0.95; 95%CI, 0.81–1.13; \( P \) for trend = 0.98).\(^ {25} \) Results from the Women’s Health Study (WHS) and Nurses’ Health Study (NHS) were similar.\(^ {21,24} \) In the recently published Iowa Women’s Health Study (IWHS), the results were slightly stronger; women with a total intake of ≥800 versus <400 IU per day had a RR of 0.89 (95%CI, 0.77–1.03; \( P \) for trend = 0.12).\(^ {22} \)

Results from analyses of different sources of dietary vitamin D among postmenopausal women are more ambiguous. One study\(^ {22} \) suggested that high vitamin D intake from food sources was potentially beneficial, but this relationship was not observed in the other studies.\(^ {21,24,25} \) In the WHS, an inverse relationship with postmenopausal breast cancer was suggested for vitamin D from supplements only and the results were not significant. Other findings in postmenopausal women worthy of note concern potential differences in the vitamin D-breast cancer relationship according to tumor characteristics. McCullough et al.\(^ {25} \) reported a stronger and statistically significant lower incidence of estrogen receptor-positive breast cancers in women with high vitamin D intake from foods, but no benefit for estrogen receptor-negative tumors. In contrast, Robien et al.\(^ {22} \) found a stronger relationship between vitamin D intake and estrogen receptor-negative tumors. Total vitamin D intake was associated with a significant 39% lower risk of in situ tumors, but it was unrelated to more advanced disease. In the WHS, risk was not modified by any tumor characteristics.\(^ {21} \)

In the two prospective studies that considered premenopausal breast cancer, the story is somewhat different (Table 1). In the WHS, women in the highest quintile of total vitamin D intake (≥548 IU per day) had a marginally significant 35% lower risk of premenopausal breast cancer than those in the lowest quintile (≤162 IU/day) (RR, 0.65; 95%CI, 0.42–1.00; \( P \) for trend = 0.07).\(^ {21} \) Risk was also lower in women consuming ≥400 IU from supplements versus those with no supplemental vitamin D, while dietary vitamin D was unrelated to risk.

In the NHS, both total vitamin D and vitamin D from food sources were inversely associated with premenopausal breast cancer; compared to those reporting ≤75 IU/day of vitamin D from foods, women receiving >300 IU/day had an RR of 0.66 (95%CI, 0.43–1.00; \( P \) for trend = 0.02).\(^ {24} \) Also of note, in the WHS a protective effect of total vitamin D intake was more pronounced in estrogen and progesterone receptor-positive tumors, tumors >2 cm, and poorly differentiated tumors.\(^ {20} \)

Taken together, these prospective studies perhaps raise more questions about the relationship between vitamin D and breast cancer than they answer. Three important questions for consideration are as follows: 1) Does vitamin D from food sources have the same effect on breast cancer development as vitamin D from supplements? 2) Does vitamin D affect premenopausal and postmenopausal breast cancer similarly? 3) When is the optimal time to assess vitamin D intake with respect to breast cancer development?

**VITAMIN D FROM FOOD SOURCES VERSUS SUPPLEMENTS**

There is clearly ambiguity in the results from prospective studies as to whether vitamin D from food sources is related differently to breast cancer development than vitamin D from supplements, or whether intake of vitamin D from all sources (i.e., total vitamin D) is the most important measure. This issue is complicated by variation in the type of vitamin D present in different foods and supplements. Though both vitamin D2 and D3 are used for supplements and in the fortification of foods including dairy products, these different types of vitamin D may not be equivalent in their effect on circulating 25OHD levels. For example, clinical studies by Harris et al.\(^ {26,27} \) have evaluated the effect of vitamin D2 and D3 supplementation on 25OHD levels in younger and older men. Younger men supplemented with 1800 IU per day of vitamin D2 for 3 weeks experienced a larger change in total 25OHD levels than older men receiving the same regimen.\(^ {26} \) In contrast, daily supplementation of 20 µg/day (i.e., 800 IU) of vitamin D3 for 8 weeks increased 25OHD levels similarly in both younger and older men compared to non-supplemented controls.\(^ {27} \) Similar results were observed in another study of younger male and female volunteers (mean age = 38 years). In that study, vitamin D3 supplementation resulted in 70% greater 25OHD concentrations than D2 supplementation.\(^ {28} \)

Laboratory analyses also indicate there can be large inconsistencies in the actual amount of vitamin D present in foods. Holick et al.\(^ {29} \) assessed 42 samples of milk purchased at supermarkets in five eastern US states and found that 71% of samples contained less than 80% or...
more than 120% of the vitamin D content stated on the package label. Similar inconsistencies were observed in subsequent studies conducted in other US states\textsuperscript{30,31} and Canada.\textsuperscript{30,32} Chen et al.\textsuperscript{33} recently evaluated the vitamin D content of various fatty fish species, as well as the effect of cooking method. They observed a nearly 4-fold difference in vitamin D level between farmed and wild-caught salmon (249 vs. 981 IU per 3.5 oz). While microwaving and baking did not substantially change the vitamin D content of farmed salmon, frying reduced the content by 49% (274 vs. 142 IU per 3.5 oz).

Because of the potential heterogeneity in the vitamin D content of foods and supplements, in any population there may be large variation in actual vitamin D intake, even among women who are consuming similar amounts of similar foods. Differences between populations and over time may also be substantial. It is unknown how much misclassification in vitamin D intake results from this heterogeneity, and to what extent the relative risks may be attenuated. The association between dietary vitamin D may be stronger in populations with a higher proportion of intake from vitamin D\textsubscript{3} than D\textsubscript{2} or in which fish intake, which provides mostly D\textsubscript{3}, contributes a much greater amount to the calculation of vitamin D.

An additional concern is the possibility that the action of vitamin D on breast cancer development is modified by calcium intake. Several of the prospective studies observed inverse relationships between calcium and breast cancer risk, possibly stronger in premenopausal\textsuperscript{21,24} and postmenopausal women.\textsuperscript{25} Results from those studies also suggest that calcium and vitamin D intake in postmenopausal women; women in the highest categories of both calcium and vitamin D had a non-significant 35% lower risk of breast cancer than those with a low intake of both.\textsuperscript{21} Thus, it is important to consider vitamin D intake in the context of calcium intake whenever possible.

Because of the likelihood of misclassification of vitamin D intake and potential inter-individual differences in vitamin D metabolism, additional prospective studies using biochemical markers of vitamin D status are needed. 25OHD is very sensitive to vitamin D intake and is used clinically to assess vitamin D sufficiency. Because plasma 25OHD reflects the actual vitamin D dose absorbed from foods and metabolized by each individual, as well as vitamin D synthesized in the skin, studies using plasma 25OHD as a biomarker of vitamin D status are generally more accurate in their categorization of participants than those using only estimated vitamin D intake. This is optimal if the ultimate goal is to assess a subject’s vitamin D status, but not ideal if the goal is to assess specifically how dietary intake relates to risk of disease. Studies assessing 25OHD are not without their own limitations, as 25OHD levels measured at a single time point may not reflect long-term vitamin D status and may need to be repeated during follow-up. To date, only one prospective study measuring 25OHD levels has been conducted, with the results suggesting a modestly reduced risk of breast cancer, especially in older women.\textsuperscript{34}

**VITAMIN D AND PREMENOPAUSAL VERSUS POSTMENOPAUSAL BREAST CANCER RISK**

Results from recently conducted large prospective studies have also differed in their estimates of the effect of vitamin D on breast cancer. There may, in fact, be true biologic differences in the etiologic effect of vitamin D. It has been proposed that vitamin D and calcium may interact in the growth of tumors expressing insulin-like growth factors (IGFs).\textsuperscript{9,10,35} Because IGF levels decline with age, the effect of vitamin D on IGF-related tumor development may be more pronounced in premenopausal compared to postmenopausal women. As discussed above, data have also suggested that calcium and vitamin D may interact in older women more than in younger women, with postmenopausal women only experiencing a lower risk of breast cancer if their calcium intake is also high.

Alternative explanations for these differences are also possible. As discussed above, to some extent inconsistencies in the results according to menopausal status may be explained by age-related impairment in the metabolism of vitamin D\textsubscript{2}. Because vitamin D\textsubscript{2} metabolism decreases with age, older women may require a substantially larger amount of dietary vitamin D\textsubscript{3} to achieve the same 25OHD levels as younger women and to derive the same benefit with respect to breast cancer. Differences in results by menopausal status may be due in part to the fact that relatively few older women consume enough vitamin D to achieve an observable benefit. Of the studies conducted in postmenopausal women, the strongest protective effect of vitamin D was observed in the group that had the highest level of vitamin D intake. Robien et al.\textsuperscript{22} found a non-significant 45% lower breast cancer risk associated with vitamin D intake of ≥800 IU per day from foods, though only 153 of 34,321 study participants achieved this level of intake.

The hypothesis that postmenopausal women may have a lower risk of developing breast cancer if vitamin D intake is sufficiently high is further supported by results from a prospective study using plasma vitamin D metabolites to assess vitamin D status.\textsuperscript{34} In the Nurses’ Health Study, 25OHD levels were found to be inversely...
and linearly associated with breast cancer incidence in women aged ≥60 years who were followed for 6 years. Risk was 36–43% lower in women in the highest three quintiles of 25OHD (≥ approximately 30 ng/mL) compared to those in the lowest quintile (< approximately 20 ng/mL). This level would be difficult to achieve through diet alone; Garland et al. estimate that, in the absence of sun exposure, women would need to consume at least 1800 IU per day of vitamin D3 to achieve plasma 25OHD levels ≥30 ng/mL. Overall, the results of prospective studies observing a relationship between vitamin D and breast cancer in premenopausal women are encouraging, in that they suggest a high vitamin D dose may be protective against the disease but imply that older women are just not reaching this level of intake.

The effect of total vitamin D on risk may also differ by menopausal status because this measurement may mean different things in different age groups. In premenopausal women, among whom supplement use is relatively uncommon, the majority of total vitamin D is likely to be from food sources. In postmenopausal women, who more commonly take supplements, a greater proportion may be from multivitamins, vitamin D supplements, and combined vitamin D/calcium supplements. Furthermore, in premenopausal women, the characteristics of women who take supplements containing vitamin D may be very different from women who do not use supplements. Supplement users may know they have low bone density or low vitamin D levels and/or may have a family history of osteoporosis. Women with these characteristics could plausibly have lower estrogen levels than women without them, and lower estrogen levels would consequently put them at lower risk for breast cancer. Thus, a beneficial effect of supplement use in premenopausal women may reflect a difference in the underlying risk of breast cancer. Ideally, future studies should also consider adjusting for plasma estrogen levels, when possible, to further reduce the possibility of confounding.

Finally, a stronger protective effect of dietary vitamin D in premenopausal women may be confounded to some extent by sun exposure, if the correlation of dietary vitamin D intake and vitamin D from sun exposure varies by age. In general, correlations between dietary vitamin D intake and plasma 25OHD levels have been relatively low, suggesting that dietary intake and sun exposure may not be well correlated. It is unknown whether correlations differ by age group. It is plausible that premenopausal women with high vitamin D intake have more physically active lifestyles than those with low intake; consequently, they may have higher sun exposure. This relationship may be less strong in older women, in whom subcutaneous vitamin D production is also somewhat impaired, further lowering the correlation between dietary intake and skin production.

The prospective studies reviewed here have attempted to control for such confounding by adjusting for physical activity and other proxies for sun exposure such as farm residence. McCullough et al. additionally stratified according to UV index in each subject’s state of residence and found that a protective effect of dietary vitamin D was stronger in women from states with a low UV index (>300 vs. ≤100 IU per day = 0.81; 95%CI, 0.67–0.97). In contrast, risk was not lower in states with a high UV index (1.05; 0.82–1.35; P for interaction = 0.05). In stratified analyses in the NHANES study, breast cancer risk was 25–29% lower in women with high dietary intake and/or high sun exposure compared to those with both low intake and low sun exposure; these results were stronger than those from studies that did not take sun exposure into consideration. Holick estimates that daily exposure of 50% of the skin for 12 minutes during midday hours in white women living at mid US latitudes would be equivalent to receiving a dietary vitamin D intake of 3000 IU per day. Thus, even minimal sun exposure contributes substantially to plasma 25OHD and may introduce substantial confounding in the assessment of dietary intake and cancer risk if not taken into consideration. Further evaluation of the correlation between dietary vitamin D intake and sunlight exposure in premenopausal and postmenopausal women would be worthwhile.

TIMING OF VITAMIN D ASSESSMENT WITH RESPECT TO TUMOR DEVELOPMENT

In general, a protective effect of vitamin D on breast cancer has been more evident in studies with shorter time intervals between vitamin D assessment and tumor development. Robien et al. addressed this issue directly by evaluating the effect of total vitamin D intake on risk while stratifying according to the length of the interval between dietary measurement and breast cancer diagnosis (Figure 1). For tumors diagnosed 0–5 years after vitamin D intake assessment, the RR for those receiving ≥800 IU per day was 0.66 (95%CI, 0.46–0.94; P for trend = 0.02); the RR increased linearly with each 5-year increase in follow-up duration to a RR of 1.23 for 15 or more years of follow-up (95%CI, 0.86–1.75; P for trend = 0.26).

Results from the other studies are largely consistent with this finding. In the WHS, women aged ≥45 years were enrolled at baseline between 1993 and 1995 and then followed until 2004 for disease development. While the average duration of follow-up was 10 years, the interval between vitamin D intake measurement and cancer diagnosis in premenopausal women was likely
only 0–3 years, as the average age of menopause in this population was approximately 48 years. In contrast, postmenopausal cases had the opportunity for a longer period between measurement and diagnosis. In the NHS, Shin et al. estimated breast cancer risk using a single vitamin D intake assessment at baseline (1980) as well as results using a cumulative averaged model, which took into consideration changes in vitamin D intake during the 16-year follow-up period; with this model, data from as many as five other food frequency questionnaires were used. Results taking the more recent assessments into consideration were significant for premenopausal women, while results using the 1980 baseline assessment only were essentially null. In postmenopausal women, results from both types of analysis were similar. The NHANES and CPS II Nutrition Cohort studies, which each used single assessments of vitamin D intake and had follow-up periods of 12 and 20+ years, respectively, reported considerably weaker associations.

Taken together, these findings suggest the following two possibilities: 1) the effect of vitamin D on tumor development is quite immediate in its timing; and/or 2) vitamin D intake is variable enough that a single measurement is insufficient to accurately characterize individuals over a long follow-up period. Lin et al. cite ample in vitro data indicating that vitamin D may have a beneficial effect in the late stages of breast tumor development, as well as on early events. Other findings consistent with this are from the WHS, suggesting that vitamin D may affect aggressive and less invasive tumors differently. In that study, a somewhat stronger protective effect of high total vitamin D intake was observed on risk of tumors with lymph node involvement, tumors >2 cm in size, or poorly differentiated tumors in premenopausal women. While vitamin D may, in fact, act at a late stage of tumor development, it is also possible that the interval between diet assessment and diagnosis may have been shorter in women with aggressive cancers as compared to those with slower growing tumors. Consequently, dietary vitamin D may have been assessed at a more etiologically relevant time period during tumor development. Additional studies exploring the timing of vitamin D assessment with respect to cancer development are clearly needed to further address these questions.

CONCLUSIONS

The relationship between dietary vitamin D and breast cancer is an important issue. Prospective studies provide the best opportunity to evaluate the relationship between dietary vitamin D intake and breast cancer.
Taken together, the five studies conducted to date suggest that vitamin D intake may, at least modestly, reduce the risk of breast cancer in younger and older women. However, the heterogeneity of results with respect to the source of vitamin D, menopausal status, and the timing of vitamin D assessment underscore the large amount of additional information still needed before the relationship is well understood. Additional prospective analyses of breast cancer and vitamin D are clearly needed. Future studies should evaluate plasma 25OHD levels in addition to dietary intake data at multiple times during follow-up.

REFERENCES

29. Holick MF, Shao Q, Lin WW, Chen TC. The vitamin


