The active metabolite of vitamin D [i.e., 1,25(OH)₂D] is a recognized modulator of cell proliferation and differentiation (1,2), and studies (3) have shown that it can reduce the incidence of mammary cancer in rats. Several mechanisms have been postulated for a protective effect of vitamin D on human breast cancer (3–8); however, epidemiologic studies (9–17) investigating dietary sources of vitamin D—and milk consumption in particular—have yielded inconsistent results in relation to breast cancer risk. Sunlight, the other source of vitamin D, has been postulated to exert a protective effect on the development of breast cancer on the basis of an ecologic correlation of age-adjusted breast cancer mortality rates and solar radiation exposure levels (5,18,19).

The metabolites of vitamin D₃ (cholecalciferol), originating from sunlight, and the metabolites of vitamin D₂ (ergocalciferol), originating from dietary sources, are indistinguishable. Therefore, measurement of 1,25(OH)₂D, the active metabolite and presumably the form through which any protective effect of vitamin D on breast cancer would operate, can be used to test this hypothesis. One previous human case-control study (20) of serum vitamin D measured after the diagnosis of breast cancer found lower levels among the case subjects.

We compared prediagnostic serum levels of 1,25(OH)₂D among women later diagnosed with breast cancer with serum levels in women who were cancer free, taking into account their exposure to recognized breast cancer risk factors. The study participants were female members of the Kaiser Permanente Medical Care Program (KPMCP) in Northern California who had taken a voluntary multiphasic health checkup (MHC) between 1964 and 1972 (21). Individuals taking the MHC were instructed to fast overnight before collection of a blood specimen and questionnaire information. Sera were frozen and stored at −23°C or colder from the time of collection until 1980, when they were transferred and stored at −40°C (22). The research protocol was approved by the Institutional Review Board of the KPMCP, Northern California Region. Among approximately 95,000 women who took the MHC, 2131 individuals developed breast cancer while still in the health plan through 1991. We designed a nested case-control study using a randomly selected sample of 96 women from a total of 1276 white women who developed breast cancer at 55 years of age or older.¹ One control subject per case subject was selected from white women in the same MHC cohort; the control subjects were matched to the case subjects on the basis of date of joining the health plan (±1 year), year of the MHC examination and age at examination, and duration of follow-up. Questionnaire data were abstracted from the MHC, and medical records were reviewed by use of a standardized form, with blinding as to the woman’s case or control status. With a sample size of 96 matched pairs, determined by the size of a main study [Moorman PG, Hulka BS, Hiatt RA, Krieger N, Newman B, Vogelman J, et al.: manuscript in preparation; (23)], we had 80% power to detect a difference of 3.8 pg/mL in mean serum levels of 1,25(OH)₂D, using a two-sided test and a significance level of α = .05 and assuming a moderate within-pair correlation of .3 and a standard deviation of 12.7 pg/mL (24). Study subjects had an average age of 51 years (standard error [SE] = 1.0 year) at the time of the MHC and an average age of 66.3 years (SE = 0.9 year) at breast cancer diagnosis. The average length of follow-up was 15.4 years (SE = 0.6 year). In these data, recognized risk factors were generally not statistically significantly associated with breast cancer, but most of the available risk factors exhibited apparent associations of the expected magnitude and in the expected direction (data not shown).

Aliquots of sera were analyzed only for 1,25(OH)₂D and not for 25 hydroxyvitamin D because of limited amounts of sera. We were also concerned that 25 hydroxyvitamin D would be more subject to seasonal variation, which we could not control. Laboratory analysis of 1,25(OH)₂D was performed in the absence of information about the study subjects, including their case or control status, by use of a calf thymus assay described elsewhere (25,26). Intra- and inter-assay coefficients of variation for this assay average 8.6% and 19.8%, respectively. The reference range for 1,25(OH)₂D with this assay is 16–42 pg/mL.

To adjust for the effects of desiccation in some of the specimens, the 1,25(OH)₂D levels were multiplied by a ratio of the normal serum sodium value of 145 mg/dL to the subject’s measured serum sodium value. Adjusted values averaged 41.9 pg/mL (SE = 1.0 pg/mL), and 90% of the values ranged between 19.8 and 66.0 pg/mL.

We found almost no difference in the prediagnostic levels of 1,25(OH)₂D between the case subjects and their matched control subjects. The mean matched-pair difference was 0.47 (95% confidence interval = −2.66 to 3.60) (Table 1). Differences in 1,25(OH)₂D levels between the case and control pairs were distributed evenly in a range between approximately −40 and 40 pg/mL.

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of 1,25(OH)_2D values found in the specimens is somewhat higher than expected (a mean of 42 instead of 32 pg/mL), although not outside a reasonable range. However, a systematic bias in the way specimens were stored over the years is unlikely. In addition, since case subjects and control subjects were matched on the basis of year of examination and length of follow-up and, since specimens were analyzed blinded and simultaneously, it is highly unlikely that any systematic bias masked a true difference in 1,25(OH)_2D levels. Finally, the credence of our results is enhanced by a previously published study (27) that used the same assay, the same laboratory, and the same Kaiser Permanente bank of stored sera and showed an association between serum vitamin D levels and prostate cancer risk.

In conclusion, we find no relationship between breast cancer and serum levels of vitamin D at an average of 15 years before the clinical diagnosis of cancer. Our study does not adequately address a possible protective effect of serum vitamin D at a time more proximal to clinically evident breast cancer.

References

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Notes

1 This study was restricted to postmenopausal white women because there were relatively small numbers of premenopausal women and women of color.

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