Scientists vary in their approaches to interpreting data. Still, we are concerned that Freedman et al. (1) rejected evidence of a substantial protective association of serum 25-hydroxyvitamin D (25(OH)D) on mortality rates from breast cancer due to incorrect use of a statistical procedure.

The mortality rate from breast cancer was statistically significantly lower in women whose serum 25(OH)D was at or above the median, 62.5 nmol/L, compared with those who were below it: the relative risk was 0.28 (95% confidence interval = 0.08 to 0.93). The confidence interval corresponds to P < .05 and met the authors’ criterion for statistical significance.

In studies of 25(OH)D and risk of cancer, odds ratios or rates are usually provided in categories, and a χ² test is used to determine whether there is an association of serum 25(OH)D with cancer risk. It is common to compare the highest with the lowest category (2–4). Freedman et al. (1) performed such an analysis by dividing the women in their study into two categories
according to 25(OH)D level and found the inverse association described above.

They then tested for linearity of trend of the association of continuous values of 25(OH)D with risk of breast cancer. The relative risk per 50 nmol/L of 25(OH)D was 0.83 and not statistically significant. The authors rejected the importance of the finding from the categorical analysis and justified this decision based on the test for trend and their concern about sample size, despite the statistical significance of the finding. Although, according to the Journal guidelines, the abstract should “concisely state all important findings of the study,” the finding from the categorical analysis regarding breast cancer was not included there.

This was not a correct decision. The interquartile range of 25(OH)D observed by Freedman et al. (1) was approximately 50–80 nmol/L (1). Because a previous cohort study (2) provided evidence of a threshold effect for breast cancer, it was not logical for Freedman et al. (1) to use a test that assumes a linear association. Three-quarters of the continuous 25(OH)D values observed by Freedman et al. (1) were in the region of the dose–response curve, 0–80 nmol/L, that is expected to be virtually flat (2). Tests for linear trend only assess the degree to which data points fit a linear model compared with the null hypothesis in which the data points fit a line with a slope of zero (5). Because most of the data points were distributed along an interval for which the slope was expected to be zero, the use of the linearity test was inappropriate (5).

On the other hand, a test of linear trend was reasonable for colon cancer because the 25(OH)D values were in an interval that began at 55 nmol/L and in which the dose–response curve for colon cancer was linear and of negative slope. This 25(OH)D level is substantially lower (6) than the threshold (80 nmol/L) above which there is an inverse relationship between 25(OH)D and breast cancer risk (2).

Despite these analytical considerations, the work by Freedman et al. (1) adds important evidence to recent studies reporting that lower serum 25(OH)D levels were associated with higher risk of breast cancer (2–4) and a clinical trial that reported similar results for all cancers (7).

References

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Response
We appreciate the opportunity to address comments by Garland et al. and Grant regarding our recent publication on vitamin D and breast cancer mortality. Garland et al. contend that we should have highlighted as “important” our finding of a statistically significantly lower risk of breast cancer mortality in women with higher (≥62.5 nmol/L) levels of 25(OH)D and that we were incorrect to examine the linear trend in breast cancer mortality risk, which we determined was not statistically significant. As we said in the paper, we felt that it would be unwise to draw strong inferences about the categorical comparison, given the small number of cases involved (ie, a total of only 28 cases, with only eight in the higher category). Because of the necessarily arbitrary cut-point between the two categories (<62.5 and ≥62.5 nmol/L), we maintain that it was useful to examine the statistical significance of the trend in risk related to continuous incremental changes in serum vitamin D level. Also, given the small number of cases, we had low power to characterize specifically the dose–response relationship between serum vitamin D levels and breast cancer mortality risk in our data. Moreover, the study of breast cancer risk cited by Garland et al. as evidence of a threshold effect is a single study of breast cancer incidence risk, was interpreted by its authors as raising only “the possibility” of a threshold (1), and was evaluated using a linear trend across quintiles.

In his letter, Grant does not question the methods in our analysis; rather, he concludes that other studies, principally ecologic studies with neither individual vitamin D nor UV-B exposures, are more persuasive. Grant, however, does not acknowledge a major problem with ecologic designs—the inability to adjust for confounders at the individual level—or that this limitation could have contributed to spurious results. There is a need for additional studies with large numbers of 25(OH)D samples to help clarify the relationship between vitamin D and cancer risk.

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