Vitamin D for cancer prevention: valid assertion or premature anointment?

Dear Sir:

Lappe et al (1) recently conducted a randomized clinical trial (RCT) that evaluated the effect of calcium or calcium + vitamin D supplementation on cancer incidence as a secondary outcome. The RCT was originally designed to compare the effect of calcium or calcium + vitamin D supplementation on skeletal status and calcium economy in postmenopausal women. The authors concluded that calcium + vitamin D supplementation was superior to placebo in overall cancer prevention in postmenopausal women. However, insufficient information and limitations of the study may require a more subdued interpretation of the results than originally purported.

The authors did not provide key information, such as demographic and baseline risk factor distributions, on the randomized groups. Such information would have allowed for further evaluation of the randomization procedures and confirmed equivalent distributions between comparison groups. Furthermore, it would have been useful to have provided detailed information regarding loss to follow-up in the treatment group, compliance characteristics by treatment group, and details regarding the per protocol analysis for both treatment groups. Treatment-specific compliance is of particular interest because of potential differential misclassification of the exposure (intervention). For example, even 10% noncompliance by the calcium + vitamin D participants who did not develop cancer may overestimate (bias away from the null) the protective effect of calcium + vitamin D supplementation by 21% [reported crude risk ratio (RR) for study period, assuming complete follow-up: 0.42; 95% CI: 0.21, 0.83; crude RR after correction for 10% misclassification: 0.53; 95% CI: 0.27, 1.06]. However, we offer only theoretical speculation that cannot be evaluated without additional information. Therefore, we recommend that future investigations adhere to the standardized CONSORT guidelines for reporting RCT results to avoid the exclusion of such necessary information (2).

The authors used logistic regression to calculate effect estimates after citing the potential for violating the proportional hazard assumption required for standard time-to-event analysis. However, the logistic regression model assumed complete follow-up despite evidence to the contrary and presented effect estimates based on cumulative incidence. Logistic regression models in this scenario may present biased estimates because of a failure to account for various forms of loss to follow-up (3). The authors did not explicitly show a violation of the assumptions of a proportional hazards model, and it is unclear why a time-dependent Cox proportional hazard model with relevant product terms was not used to verify the assumption in question (3). Model selection (whether time-dependent or a standard proportional hazard) could have proceeded accordingly if the assumption were indeed violated. Furthermore, even a standard Cox proportional hazard model would have provided more precise estimates than a logistic regression model, regardless of the proportional hazard assumption, because it would still allow for censoring (3), but could be interpreted as an average rather than a time-dependent hazard (risk) ratio.

Insufficient duration of follow-up may also contribute to the uncertainty of the findings. Results from an investigation of vitamin D and breast cancer risk in postmenopausal women from the Iowa Women’s Health Study were also recently released (4). Robien et al (4) reported a lower breast cancer risk for the first 5 y of follow-up in postmenopausal women with a total vitamin D intake >800 IU/d than in a reference group with a total vitamin D intake <400 IU/d (RR: 0.66; 95% CI: 0.46, 0.94). However, the risk estimate converged to null after 10 y of follow-up, and the higher vitamin D intake category eventually exceeded the risk of the reference category after 15 y of follow-up (RR: 1.23; 95% CI: 0.86, 1.75) (4). The findings by Robien et al indicate the importance of the duration of follow-up and raise a legitimate concern regarding the potential for a similar trend if Lappe et al continued follow-up for a similar duration. Furthermore, the well-established phenomenon of enhanced calcium absorption in the presence of vitamin D (5) raises uncertainty regarding the suggested independent action of vitamin D as a causal mechanism for cancer prevention (1). The results provided by Lappe et al are not capable of differentiating between molecular synergism and independent nutrient action. Future studies of calcium and vitamin D should account for biological interaction to better address causality.

The findings by Lappe et al warrant considerable speculation and require further evaluation to confirm their validity. Insufficient information regarding baseline characteristics, loss to follow-up, and compliance limit potential inferences. Furthermore, the inefficiency
to the treatment groups. This should allay the concerns of Ojha et al about potential differential misclassification of the exposure (intervention). Finally, there were no statistically significant differences between groups in the percentage of subjects completing the study (calcium-only group: 86.5%; calcium and vitamin D group: 85.4%, and placebo group: 83.3%).

Ojha et al raise questions about our statistical modeling. We remind them, and assure the Journal’s readers, that the purpose of Cox and logistic models is to increase sensitivity and that our results were sufficiently clear cut as to be evident by simple chi-square analysis, as we stated in our article. We used logistic regression mainly to refine our estimate of the effect size.

Ojha et al also states that an insufficient duration of follow-up may have contributed uncertainty to our findings. They support this concern by citing a recent observational study (2) that reported a reduced breast cancer risk associated with self-selected vitamin D intake >800 IU/d and that found that the risk estimate converged to null after 10 y of follow-up. An important congruence between our randomized study and the study by Robien et al is that a higher intake of vitamin D in both instances was associated with a dramatic decrease in the incidence of cancer within a relatively short period of time (4–5 y). Even if the long-term effect of vitamin D were simply to delay the onset of cancer, that outcome would clearly be beneficial and one that individuals at risk of cancer would accept with alacrity. However, it is unlikely to be just a delay. The reduction in cancer incidence that we reported was precisely of the magnitude found in a large number of observational vitamin D studies and meta-analyses of such studies (eg, 2–5). Moreover, the serum 25-hydroxyvitamin D concentration predicted risk as well as did the fact of treatment.

The concerns of Ojha et al about the validity of our study have no sound basis. The design of our study (population-based, random assignment, double-blind, and placebo-controlled), the low dropout rate, and the excellent compliance with treatment provide confidence that the findings are valid. Furthermore, our findings are supported by a large body of epidemiologic, observational, and case-control evidence that vitamin D decreases cancer risk. Finally, vitamin D supplementation is safe and inexpensive. We argue that it is in the public interest to strongly support optimal vitamin D nutritional status.

Neither author had a conflict of interest.

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REFERENCES

Reply to RP Ojha et al

Dear Sir:

Ojha et al voice concern that we did not provide enough key information about baseline data and compliance in our study (1) and that a more subdued interpretation of the results might be required. We remind Ojha et al that our random assignment of subjects to treatment groups was designed to eliminate systematic bias between groups with respect to attributes that might have affected the dependent variable, ie, the incidence of cancer. Randomization is a trustworthy and accepted method of allocating unrecognizable responders to the various contrast groups.

Nonetheless, we are pleased to provide additional information. There were no significant differences between the randomized groups in age, weight, height, body mass index, baseline calcium intake, use of hormones, smoking, any of the bone scan variables, prevalence of spine fracture, or any of the laboratory tests (parathyroid hormone, albumin, bone-specific alkaline phosphatase, calcium, serum 25-hydroxyvitamin D, or creatinine concentrations).

Although there was a statistically significant difference in compliance with calcium supplements between those in the calcium-only group and those in the placebo group (mean adherence: 76% compared with 82%, respectively; \( P = 0.004 \)), there were no significant differences in compliance with vitamin D supplementation between the treatment groups.