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COMMENTARY

Calcium, Vitamin D, and Risk Reduction of Colorectal Cancer

Harold L. Newmark and Robert P. Heaney

The results of two controlled intervention studies in older women using dietary supplements of calcium and vitamin D, as part of the Women's Health Initiative (WHI) studies, were reported in major medical journals, regarded as authoritative by the general public (1,2). One of these reports dealt with the effects of these dietary supplements on the risk of colorectal cancer (1). The public news media generally reported negative results as summarized in the abstracts of these articles and in the associated press releases. However, the full text of the articles contained a great deal of qualifying data, including high basal dietary intake of calcium in the subjects involved (nearly twice the U.S. average intake), vitamin D intake at close to recommended levels (at least twofold the U.S. average), low compliance with intervention (only about 70% of subjects reported more than 50% compliance), probably inadequate duration of intervention, low intervention dosage of vitamin D, and a significant 2.5-fold increase in risk of colorectal cancer in the lowest 25-hydroxy vitamin D quartile. These "qualifiers" in the authors' text were generally omitted from the journal abstracts and the media coverage. An exception was *The Wall Street Journal*, which issued a detailed and critical analysis of the publications of the WHI studies (3), and Jane Brody's article in *The New York Times*, whose message was "Read the fine print. Stay the course."

This review is intended to clarify, for readers of this journal who are concerned with the relation between diet and cancer, some of the design flaws and qualifying data of the WHI study report of the trial of calcium and vitamin D supplementation and colorectal cancer risk (1).

Some detailed comments:

1. Subjects' dietary intake plus self-administered calcium and vitamin D supplements resulted in a mean total calcium daily intake of 1,100–1,200 mg/day (nearly twice the U.S. national average for women in the age range concerned) and vitamin D intake of about 367 IU daily, slightly less than the recommended daily allowance of 400 IU (about three to four times the U.S. national dietary average) (1,2). These basal intakes on entry nearly met current recommendations (4), and the subjects were permitted to continue to take calcium and/or vitamin D supplements on their own during the course of the study, irrespective of treatment assignment.

There are major design flaws present:

a. For the dietary calcium effect on colorectal cancer, the original hypothesis was calculated to correct the current imbalance in the colon from the low mean U.S. intake of 500–600 mg of daily calcium together with the U.S. intake of 35–40% of calories as dietary fat (5). The beneficial effect of calcium in the digestive residue lies in its propensity to bind unabsorbed fatty acids and bile acids, which act as cancer promoters for the colon mucosa. The effect of dietary calcium would be expected to plateau when the full load of these cancer promoters has been complexed. This plateau was originally "guestimated" at about 1,200 mg/day of calcium. More recent studies, based on analysis of actual colorectal cancer risk versus calcium dietary intake, in large populations, have shown threshold or plateau values in the range of 1,000–1,400 mg daily calcium intake (6,7). In particular, see Fig. 1 of Ref. 7. Because the subjects on entry to the study had an intake of calcium of 1,100–1,200 mg and this diet was permitted to continue (with supplements self-selected, as before the study), supplemental calcium administered as part of the study design would not be expected to produce any additional protective response. In other words, "more is not better" beyond the threshold or plateau values, which roughly coincide with the current recommended intakes based primarily on prevention of osteoporosis by the Institute of Medicine (4).

b. The subjects enrolled in this study exhibited a strong healthy volunteer bias. The subjects were apparently receiving a significant amount of calcium and vitamin D from dietary supplements before entry into the WHI trials.

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This is particularly apparent in the data on vitamin D daily intake because food sources of vitamin D are poor and inadequate (4). Daily calcium intake, unless supplemented, or including a larger than average intake of dairy products, is also inadequate in the United States. It should be noted that a current scientific tactic in the United States is to fortify broadly consumed foods (for example, fruit juices and cereal grain products, including flour, bread, and pasta) to add about 400 mg calcium daily to the diet, at very low cost, to enable the total calcium daily intake to reach about 1,000 mg from the now-current 600 mg in the general public, without the extra cost or motivational barriers of regular use of calcium supplements.

c. Compliance of the subjects for study medication was poor: only 70% took 50% or more of the study supplements. This can be approximated as a mean intake of about 35% of the study target doses, suggesting mean intake of only about 350 mg of calcium and 140 IU vitamin D of the study supplements. The publication and the abstract should have included a per-protocol analysis as well as intention-to-treat analysis to distinguish any possible effect of the intervention as contrasted with its mode of delivery (for example, daily pill taking vs. fortification).

2. The duration of the study (average about 7 yr) was probably inadequate to affect measurable development of colon cancer, considering the current understanding of its long (10–20 yr) latency. This is discussed in the text, and also in the abstract, as an important consideration in the limitations of the study (1). This is also evident in the following statement from the text (page 690) (1):

> The hazard ratio for death from colorectal cancer was 0.82 in the supplement group as compared with the placebo group (95 percent confidence interval, 0.52 to 1.29; P=0.39); however, too few events had occurred (34 vs. 41) to make the comparison meaningful.

3. The study intervention dose of vitamin D was too low. Although this was not apparent at the time the studies were designed, more recent studies have demonstrated that effective long-term reduction of colorectal cancer risk is associated with maintenance of a serum level of 25-hydroxy vitamin D of 80 nM (or 32 mg/ml) or more, as reviewed by Gorham et al. (8,9). To achieve this serum level with minimum dependence on sun exposure requires an actual vitamin D daily dietary intake of more than 1,000 IU (10).

4. In Table 2 and page 691 of Ref. 1, the authors clearly indicated that vitamin D status of the women at baseline (as serum 25-hydroxy vitamin D) exhibited a significant inverse relationship with incident cancer risk during the study. The lowest quartile of 25(OH)D had a 2.5-fold increase in risk relative to the top quartile (*P* for trend = 0.02). However, this important observation was not mentioned in the abstract.

5. The news media mainly reported only the negative results of the abstract of the study and, largely in a sensational manner, created a misleading effect on the general public. Scientific and medical readers often read the abstracts as an entry into reading the full article. Media personnel, generally less trained medically and scientifically, and also under the pressure of time, may use the abstract or press release alone, as they largely did in this instance, with some exceptions (3). This represented poor quality of scientific communication to the general public by the media and created problems for medical and public health professionals to correct the misunderstanding in patients. Perhaps thoughtful discussions should be considered involving representatives of the media, journalism schools, and scientific, medical, and public health institutions to develop effective prevention of future inaccurate and misleading media reports on such important public health issues.

Acknowledgments and Notes

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