Risk of Prostate Cancer in a Randomized Clinical Trial of Calcium Supplementation

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Abstract

Background: In some studies, high calcium intake has been associated with an increased risk of prostate cancer, but no randomized studies have investigated this issue.
Methods: We randomly assigned 672 men to receive either 3 g of calcium carbonate (1,200 mg of calcium), or placebo, daily for 4 years in a colorectal adenoma chemoprevention trial. Participants were followed for up to 12 years and asked periodically to report new cancer diagnoses. Subject reports were verified by medical record review. Serum samples, collected at randomization and after 4 years, were analyzed for 1,25-$(OH)_2$ vitamin D, 25-(OH) vitamin D, and prostate-specific antigen (PSA). We used life table and Cox proportional hazard models to compute rate ratios for prostate cancer incidence and generalized linear models to assess the relative risk of increases in PSA levels.
Results: After a mean follow-up of 10.3 years, there were 33 prostate cancer cases in the calcium-treated group and 37 in the placebo-treated group [unadjusted rate ratio, 0.83; 95% confidence interval (95% CI), 0.52-1.32]. Most cases were not advanced; the mean Gleason's score was 6.2. During the first 6 years (until 2 years post-treatment), there were significantly fewer cases in the calcium group (unadjusted rate ratio, 0.52; 95% CI, 0.28-0.98). The calcium risk ratio for conversion to PSA >4.0 ng/mL was 0.63 (95% CI, 0.33-1.21). Baseline dietary calcium intake, plasma 1,25-$(OH)_2$ vitamin D and 25-(OH) vitamin D levels were not materially associated with risk.
Conclusion: In this randomized controlled clinical trial, there was no increase in prostate cancer risk associated with calcium supplementation and some suggestion of a protective effect. (Cancer Epidemiol Biomarkers Prev 2005;14(3):586−9)

Introduction

In contrast to likely protective effects on colorectal neoplasia (1), high intake of dietary and supplemental calcium has been associated with an increased risk of prostate cancer in some epidemiologic studies (2-5). Other investigations have reported contrary data (6-12), but no randomized clinical trial of calcium supplementation has considered prostate cancer as an end point. To clarify this association, we tested the hypothesis that calcium intake increases prostate cancer risk, by analyzing data from a multicentered, randomized double-blind clinical trial of calcium supplementation for prevention of colorectal adenomas.

Materials and Methods

In 1988, with Institutional Review Board approval, our research group began a clinical trial of calcium supplementation to prevent colorectal adenomas (1). We randomly assigned 930 participants to receive either placebo or 3 g of calcium carbonate (equal to 1,200 mg elemental calcium) daily for 4 years. Every 6 months during the scheduled 4 years of active treatment, we sent questionnaires to participants regarding their adherence to study treatment,

their use of medications and nutritional supplements, and the occurrence of symptoms, illness, and hospitalizations. We assessed diet using a validated food frequency questionnaire (13) at enrollment and at the end of the study treatment.

The treatment phase of the study ended in 1996, and in 1999, we initiated post-treatment follow-up of medical events (such cardiovascular disease, fractures, and cancer) and use of medications and nutritional supplements. Of the 672 men who were randomized, 42 died during his anticipated treatment period and 588 provided post-treatment follow-up data. Losses after the end of the 4-year intervention were due to our inability to contact 13 men, later deaths of 14, and refused follow-up for 15.

No patient had a history of prostate cancer at study entry. Incident cases were sought through the periodic follow-up questionnaires described above. All reports of prostate cancer (by questionnaire or death certificate) were verified by review of hospital records. Using the available clinical records, we also retrieved the Gleason's score and assessed whether the prostate cancer had apparently spread beyond the gland itself. All reported cases had been histologically verified.

Specimens of venous blood were collected at enrollment and upon completion of the active phase of treatment at 4 years and were stored at −70°C. Serum samples were assayed for 1,25-$(OH)_2$ vitamin D and 25-(OH) vitamin D using a competitive protein-binding assay (Quest Diagnostics, San Juan Capistrano, CA), as described previously (14). To monitor the precision of the assays, serum samples from 182 subjects were split, and the paired aliquots distributed among batches shipped for analysis. The interbatch Pearson correlation for the 25-(OH) vitamin D measurements was 0.95; for 1,25-$(OH)_2$ vitamin D, it was 0.58.

Prostate-specific antigen (PSA) measurements were made on baseline and year 4 bloods. In view of the fact that our trial participants had not been asked to consent to PSA determination and in accordance with the requirements of our Institutional Review Board, we conducted these measurements on specimens that could not be linked to individual men. We determined total serum PSA using a solid-phase, two-site chemoluminescent immunometric assay (IMMULITE PSA, Diagnostic Products Co., Los Angeles, CA) and incorporated these data into an anonymous database that included only treatment assignment, PSA results, age in 5-year intervals, and quartiles of baseline dietary calcium intake. The coefficient of variance of the assay is 6.1% at 0.21 ng/mL and 3.8% at 157 ng/mL.

Statistical Methods. Of the 930 patients randomized in the original study, 672 were men, and these individuals form the basis for our analyses. We followed an intent-to-treat approach and used life table and Cox proportional hazard models (15) to compute unadjusted rate ratios and 95% confidence intervals (95% CI) as measures of the effect of calcium supplementation on prostate cancer incidence. Subjects were followed until death or the date of last questionnaire contact before January 1, 2003. We assessed the association of baseline 1,25-$(OH)_2$ vitamin D and 25-(OH) vitamin D levels with prostate cancer risk using proportional hazards modeling adjusted for age; further analyses with adjustment for season of blood draw (four categories) did not materially affect the findings and are not presented. Associations with baseline dietary calcium intake were similarly assessed, using the residual of the regression of the log of calcium intake on the log of caloric intake as the independent variable of interest. In these analyses, log of calories and age were included as covariates. For both the vitamin D and dietary calcium analyses, models including clinical center were unstable and are not presented.

A total 542 men had both enrollment and end-of-treatment PSA levels determined. Data from these individuals form the basis for the analysis of risk of PSA conversion. We used generalized linear models to compute risk ratios for PSA conversion associated with treatment assignment, with adjustment for age and quartiles of dietary calcium. Diagnostic plots and F tests were used to access model fit. $P = 0.05$ was considered statistically significant.

Results

There were no statistically significant differences at study entry between the 327 men assigned to calcium supplements and the 345 assigned to placebo with regard to age, dietary calcium, length of follow-up, or mean serum PSA (Table 1). Among the 544 men whose PSA was determined from a baseline blood specimen, 34 of 263 (12.9%) in the placebo group and 24 of 281 (8.5%) in the calcium treated group had a PSA of >4.0 ng/mL ($P = 0.13$).

A total of 24 prostate cancers were diagnosed during the treatment phase of the trial and 46 during the subsequent follow-up. In 66 of the 70 cases, sufficiently detailed clinical records had been obtained to permit determination of the spread of the tumor; only 11 were thought to have spread beyond the capsule. Gleason's score was available for 63 subjects. The mean score ±SD was 6.2 ± 1.5; this was essentially identical in the two treatment groups (data not shown).

The cumulative incidence curves for prostate cancer suggested a reduced risk among treated patients beginning about 2 years after the start of treatment and persisting for ~2 years after treatment ended, with a subsequent convergence in the curves (Fig. 1). The rate ratio for calcium varied with the assumptions regarding latency and duration of effect after treatment cessation. Prostate cancer incidence over the entire period of study was moderately lower among the calcium-treated group than the control group (rate ratio, 0.83; 95% CI, 0.52-1.32), although this reduction was clearly compatible with a chance association. There were statistically significant reductions in prostate cancer risk between baseline and year 6 (rate ratio, 0.52; 95% CI, 0.28-0.98) and between years 2 and 6 (rate ratio, 0.44; 95% CI, 0.21-0.94).

In 47 patients, prostate cancer with a Gleason score of ≥6 was diagnosed. For these cancers, the calcium rate ratio over the entire follow-up (0.65; 95% CI, 0.36-1.17) was nonsignificantly lower than that for all cancers. We saw similar patterns over time as in the overall analysis, though with more marked reductions in risk (data not shown). There were too few cancers diagnosed with higher Gleason's scores to support a detailed analysis for more advanced end points. Over the entire follow-up, the rate ratio for the 25 prostate cancers with a Gleason's score of ≥7 was 0.70 (95% CI, 0.30-1.61).
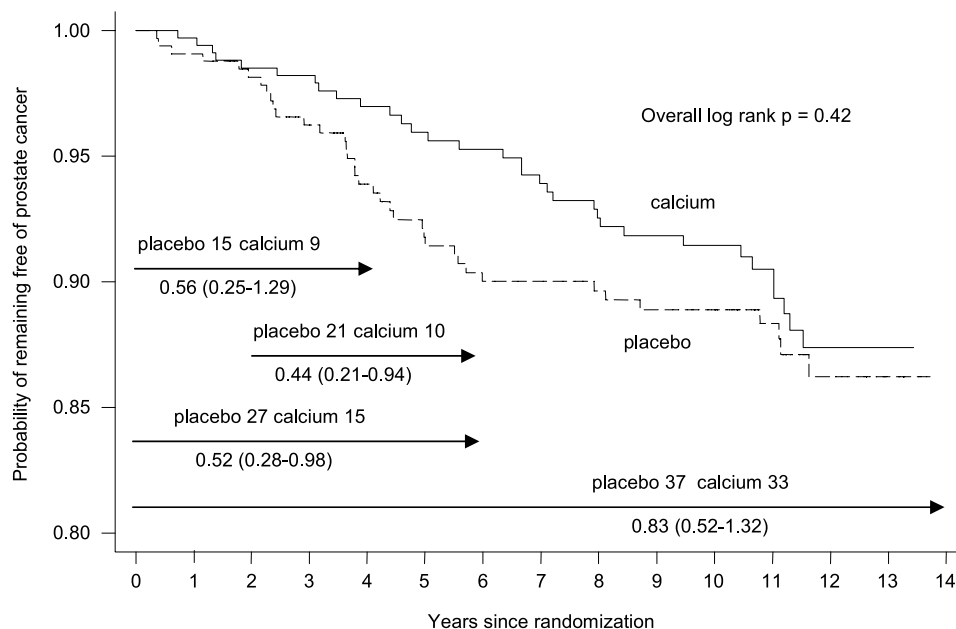
Figure 1. Kaplan-Meier plot of the prostate cancer-free status over time of men in the calcium and placebo groups. Unadjusted rate ratios with 95% CIs are provided for the intervals highlighted with the number of prostate cancers in the given interval. The original treatment phase lasted ~4 years.

Table 1. Selected comparisons between placebo and calcium groups

Variable	Placebo (n = 327)*	Calcium (n = 345)*
Age, mean ± SD (y)	61.8 ± 8.7	61.8 ± 8.6
African American race, n (%)	18 (5.5)	18 (5.2)
Months on treatment, mean ± SD	43.9 ± 7.7	44.0 ± 9.4
Months taking ≥50% of study pills, mean ± SD	38.6 ± 12.5	36.9 ± 13.8
Total months of follow-up, mean ± SD	123.8 ± 34.2	122.3 ± 36.2
Total calories (kcal)†, mean ± SD	2,139 ± 752	2,149 ± 760
Dietary calcium intake (mg)†, mean ± SD	902 ± 435	919 ± 466
Baseline PSA (ng/mL)‡, mean ± SD	1.88 ± 2.52	1.72 ± 2.93

*n includes all men who were randomized.

†Estimated from food frequency questionnaires administered at baseline for 320 men assigned to placebo and 336 men assigned to calcium.

‡Determined for 263 men assigned to placebo and 279 to calcium who had baseline and year 4 measurements.

PSA change was weakly and not statistically significantly associated with calcium supplementation. After 4 years of treatment, the PSA increased by a mean ± SE of 0.53 ± 0.18 in the placebo group and by 0.28 ± 0.19 in the calcium group ($P = 0.34$). Among men assigned to calcium supplementation, relative to those assigned to placebo, the risk ratio of converting to a PSA > 4.0 ng/mL was 0.63 (95% CI, 0.33-1.21) and the risk ratio of converting to a PSA > 6.0 ng/mL was similar (Table 2).

Among the 483 men who had serum vitamin D concentrations determined at randomization and after 4 years of study, serum $1,25\text{-}(OH)_2$ vitamin D concentrations decreased from 42.9 to 41.2 pg/mL in those assigned to receive calcium supplementation and increased from 43.4 to 44.8 pg/mL in those assigned to placebo ($P = 0.03$). There were small (3-4%) decreases in 25-(OH) vitamin D levels in both treatment groups (data not shown).

There were no substantial associations of baseline serum vitamin D concentrations with prostate cancer risk (Table 3). Mean ± SE baseline $1,25\text{-}(OH)_2$ vitamin D levels were 43.9 ± 1.8 pg/mL among individuals later diagnosed with prostate cancer and 43.1 ± 0.6 pg/mL in those who were not ($P = 0.68$). The corresponding means ± SE for 25-(OH) vitamin D were 31.5 ± 1.4 ng/mL and 29.8 ± 0.5 ng/mL respectively ($P = 0.25$). There was also no material association of baseline dietary calcium intake with prostate cancer risk (Table 3).

Discussion

An association between high intake of calcium and prostate cancer risk has been reported in several cohort (2-4) and case-control (5, 16) studies. In these investigations, the increase in risk has been seen with both dietary (largely dairy; ref. 2, 3, 5, 16) and supplemental (2) calcium and has seemed greater for advanced tumors (2, 5, 16). However, no clear association was noted in other cohort investigations (6-8), and results from case-control studies have also been conflicting (9-12). The increase in prostate cancer risk in association with high calcium intake has been hypothesized to result from a calcium-mediated reduction in the formation of $1,25\text{-}(OH)_2$ vitamin D from 25-OH vitamin D in the kidney (17).

In our randomized trial, the incidence of prostate cancer was clearly not elevated and was possibly lower among men assigned to calcium supplementation. Moreover, calcium supplements were not associated with an increased risk of PSA conversion, a possible marker of preclinical cancer. Dietary calcium intake was similar in both groups at the time of randomization, and the prescribed dose of calcium supplementation was sufficient to lower serum concentrations of $1,25\text{-}(OH)_2$ vitamin D, albeit slightly. Adjustment for baseline covariates did not change our conclusions in any meaningful way. Thus, our results provide reasonably strong evidence against the hypothesis that calcium intake materially increases overall prostate cancer risk.

The graph of cumulative prostate cancer incidence (Fig. 1) showed no difference between the trial groups in prostate cancer risk for the first 2 years after randomization, a finding that is consistent with a delayed effect of supplemental calcium. The curves for the two groups began to converge 2 years after the end of supplementation perhaps indicating that a beneficial effect of calcium requires continued treatment.

Evidence that $1,25\text{-}(OH)_2$ vitamin D inhibits prostate cancer comes from several sources. For example, vitamin D receptors are present in prostate cells and $1,25\text{-}(OH)_2$ inhibits cell proliferation (17). In addition, mortality from prostate cancer is lower in sunnier regions of the US, where increased exposure to UV light would plausibly increase synthesis of vitamin D (18). Data from one case control study indicated that prediagnostic serum concentrations of $1,25\text{-}(OH)_2$ vitamin D were lower among prostate cancer cases than controls, although this finding pertained only to older men (19), and other studies have found no association (20-22). In aggregate, findings from observational studies regarding blood concentrations of 25-(OH) vitamin D do not strongly suggest a material association with prostate cancer (19-24).

In our trial, the mean serum concentration of $1,25\text{-}(OH)_2$ vitamin D fell by only 4% after 4 years of calcium supplementation. This change was statistically significantly different from the 3% mean increase in concentrations found among men assigned to placebo, but it was perhaps too slight to result in any measurable change in cancer risk. The lower precision of the $1,25\text{-}(OH)_2$ vitamin D assay further limits interpretation of this finding. Thus, our results bear more directly on the question of the association of calcium intake with prostate cancer risk than on the possible protective effects of vitamin D.

It is not clear how oral calcium supplementation might lead to a decrease in prostate cancer risk. Prostate cancer cells have been found to express the calcium sensing receptor (25, 26), but calcium supplementation in healthy individuals results in only a small, transient increase in serum calcium levels (27), which seem unlikely to modulate carcinogenesis in the prostate. On the other hand, calcium supplementation decreases parathyroid hormone levels. This hormone has been proposed to have proneoplastic effects, possibly through increases in levels of insulin-like growth factor I (28).

In contrast to the possible inverse relationship seen with randomized treatment with calcium supplements, there was no association between estimated dietary calcium intake at baseline and risk of prostate cancer. Indeed, the direction of the relationship was, if anything, in the opposite direction. These associations are not directly comparable, if only because of the substantial differences in the amount of calcium intake involved.

Table 2. Relative risk of conversion to an elevated PSA between baseline and year 4 using 4 and 6 ng/mL cutoff points

Cut point (ng/mL)	Placebo (n = 263), n cases (%)	Calcium (n = 279), n cases (%)	Risk ratio (95% CI)
>4	21 (8)	14 (5)	0.63 (0.33-1.21)
>6	13 (5)	10 (4)	0.73 (0.32-1.63)

NOTE: PSA concentration determined at both baseline and year 4 for 263 men assigned to the placebo group and 279 to the calcium group.

Table 3. Relationship between prostate cancer risk and baseline dietary calcium intake and baseline serum concentrations of 25-OH and 1,25-OH vitamin D

	Rate ratio (95% CI)			
	Tertile I	Tertile II	Tertile III	*P* for trend
Dietary Calcium*	1.00 (reference)	1.48 (0.81-2.70)	1.20 (0.64-2.23)	0.51
Serum 25-OH vitamin D[†]	1.00 (reference)	1.22 (0.66-2.26)	1.32 (0.72-2.43)	0.70
Serum 1,25-OH vitamin D*	1.00 (reference)	1.00 (0.55-1.83)	1.02 (0.57-1.85)	0.92

NOTE: Prostate cancers from randomization to end of follow-up.

*Tertiles based on log-log residuals form regression of dietary calcium intake on energy intake; Rate ratio adjusted for age, treatment and log-calories.

[†]Rate ratio adjusted for age and treatment; Cut points between tertiles 1 and 2 and tertiles 2 and 3 for dietary calcium (assuming 2,000 kcal intake): 675.2, 990.8; for 25-OH vitamin D: 25.2, 34.0 ng/mL; for 1,25-OH vitamin D: 36.4 and 47.08 pg/mL.

When speculating about the existence and features of a protective effect of supplemental calcium, several limitations of our study should be taken into account. We did not anticipate the possibility of a protective effect on prostate cancer when we designed our study, and these findings have emerged only in secondary analyses. The only nominally statistically significant inverse associations between calcium and prostate cancer risk were found in the analyses with data truncated at the sixth year of follow-up. Lastly, there were fewer men with an elevated baseline PSA in the group assigned to calcium than in the placebo group, and this imbalance may have contributed to the apparently lower risk of prostate cancer seen in subsequent years. Because of the Institutional Review Board restrictions on our analysis, it is impossible for us to investigate this issue further. For all of these reasons, the play of chance is a possible explanation for the risk differences that we found. In addition, the overwhelming majority of the prostate cancer cases in our cohort had localized tumors; our data do not provide meaningful information regarding the effect of calcium supplementation on advanced prostate cancer.

We had complete data on PSA serum concentrations for only 542 (81%) of the 672 men randomized, and in accordance with the requirements of our Institutional Review Board, we analyzed data on PSA anonymously. Thus, our database may have been too limited to allow a detailed analysis of the possible effects of supplemental calcium on this cancer marker. In addition, some enrolled trial participants were treated for prostate cancer between randomization and the year 4 blood specimen collection, probably causing their PSA values in year 4 to be lower than they otherwise would have been. Nevertheless, we found no evidence that calcium supplementation was associated with development or progression of occult prostate cancer, as reflected in the calculated risk of PSA conversion. Again, the observed risk was lower, although not statistically significantly so, in the men assigned to calcium supplementation.

In summary, our data do not support the hypothesis that calcium supplementation increases the overall risk of prostate cancer, and they raise the possibility that calcium may, in fact, lower risk of this cancer. Further investigation is clearly warranted, particularly for advanced prostate cancers, because our study could not address the effect of calcium supplementation on those tumors.

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BLOOD CANCER DISCOVERY

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Cancer Epidemiol Biomarkers Prev 2005;14:586-589.

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