

Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial

Weronika Dyszkiewicz, Katarzyna Mamla

Faculty of Mathematics and Information Science
Warsaw University of Technology

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Title: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial

Authors: Joan M. Lappe, Dianne Travers-Gustafson, K. Michael Davies, Robert R. Recker, Robert P. Heaney

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This trial was registered at clinicaltrials.gov

Background: Numerous observational studies have found supplemental calcium and vitamin D to be associated with reduced risk of common cancers. However, interventional studies to test this effect are lacking.

Objective: The purpose of this analysis was to determine the efficacy of calcium alone and calcium plus vitamin D in reducing incident cancer risk of all types.

Study Participants

Recruitment: Participants were recruited via random telephone dialing from a 9-county rural area in eastern Nebraska.

Inclusion Criteria:

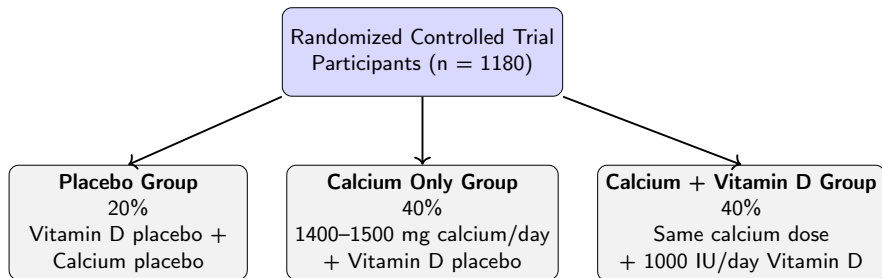
- Women aged > 55 years
- No known cancer (at enrollment or in the previous 10 years)
- Mentally and physically fit for 4-year participation

Enrollment:

- Total enrolled: 1180 women (1 excluded post-enrollment)
- Final sample: 1179 participants

Baseline Characteristics:

- Mean age: 66.7 ± 7.3 years
- Mean BMI: 29.0 ± 5.7 kg/m²
- Serum 25(OH)D: 71.8 ± 20.3 nmol/L
- 46% ($n = 543$) received prescribed estrogen for at least 6 months
- All participants were of white ancestry



Randomization:

- 1 Computer-generated permuted block design ($n = 5$).
- 2 Study nurses enrolled participants and assigned them to groups.

Supplement Distribution:

- Provided by project nurses every 6 months
- Vitamin D reordered annually, potency confirmed at start and end of year

Completion:

- 86.8% (n = 1024 out of 1180) completed the 4-year study
- Most dropouts (n = 92) occurred within the first year

Compliance with study:

- Compliance with study medication (both active and placebo) was assessed at 6-mo intervals by bottle weight.
- Mean adherence (defined as taking 80% of assigned doses) was 85.7% for the vitamin D.
- Mean adherence was 74.4% for the calcium.

Health status was assessed at 6-month intervals throughout the study.

When a participant reported a cancer diagnosis during the interval between visits, medical records were reviewed to confirm the diagnosis and to determine the primary site of the cancer. The confirmed date of diagnosis was then used to time the cancer event in subsequent statistical analyses.

Approach:

- Analysis followed the **intention-to-treat** principle.
- Also examined outcomes by serum 25(OH)D levels (baseline and 12 months).

Methods:

- **Survival analysis** used to visualize cancer incidence differences.
- **Cox proportional hazards model** was not used – assumption of constant hazard ratio over time not valid in this context.
- **Logistic regression models** was used instead to
 - Estimate relative risk (RR) of cancer
 - Explore predictors of cancer incidence (e.g., treatment, serum vitamin D levels)

Relative Risk (RR)

Definition

The relative risk (RR), also known as the risk ratio, is defined as the ratio of the probability of an outcome occurring in the exposed group to the probability of the same outcome occurring in the unexposed group

$$RR = \frac{P(\text{Outcome} \mid \text{Exposed})}{P(\text{Outcome} \mid \text{Unexposed})}.$$

Interpretation

- $RR = 1$ - Exposure does not affect the outcome.
- $RR < 1$ - The outcome is less likely in the exposed group, the exposure is a *protective factor*.
- $RR > 1$ - The outcome is more likely in the exposed group, the exposure is a *risk factor*.

Results

Site	Placebo (n=288)	Calcium Only (n=445)	Ca + D (n=446)
Breast (n)	8	6	5
Colon (n)	2	0	1
Lung (n)	3	3	1
Lymph, leukemia, myeloma (n)	4	4	2
Uterus (n)	0	2	1
Other (n)	3	2	3
Total¹	20 (6.9%)	17 (3.8%)	13 (2.9%)

Table: Cancer cases by site and treatment group (Years 1–4)

Site	Placebo (n=266)	Calcium Only (n=416)	Ca + D (n=403)
Breast (n)	7	6	4
Colon (n)	2	0	0
Lung (n)	3	2	1
Lymph, leukemia, myeloma (n)	4	4	2
Uterus (n)	0	1	0
Other (n)	2	2	1
Total¹	16 (6.8%)	15 (3.6%)	6 (2.0%)

Table: Cancer cases by site and treatment group (Years 2–4)

¹ Percentage of participants in each group who developed cancer.

Relative Risk (RR) – Intention to Treat:

- Ca + D group: RR = 0.402 (CI: 0.20–0.82, p-value = 0.013)
- Ca-only group: RR = 0.532 (CI: 0.27–1.03, p-value = 0.063)

After excluding Year 1 cases:

- Ca + D: RR drops to 0.232 (CI: 0.09–0.60, p-value = 0.005)
- Ca-only group: effect remained nonsignificant

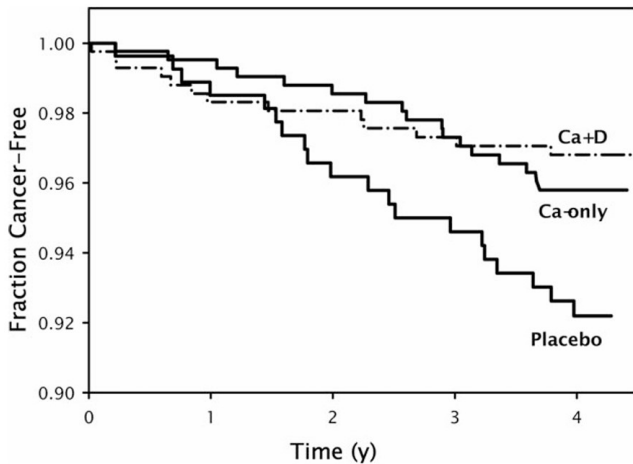


Figure: Kaplan-Meier survival curves for the 3 treatment groups.

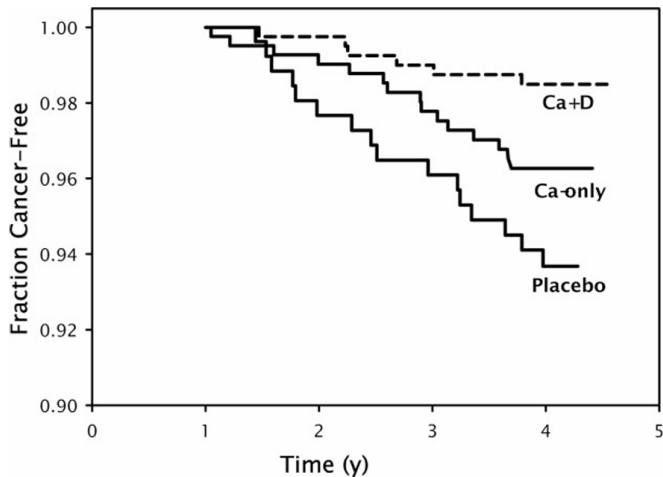


Figure: Kaplan-Meier survival curves for the 3 treatment groups randomly assigned in the cohort of women who were free of cancer at 1 y of intervention ($n = 1085$).

Logistic Regression Model:

$$\text{logit}(p) = \beta_0 + \beta_1 \cdot (\text{Treatment}) + \beta_2 \cdot (\text{25(OH)D after 12 months}) \\ + \beta_3 \cdot (\text{BMI}) + \beta_4 \cdot (\text{Age}) + \beta_4 + \epsilon$$

- Significant predictors: **Treatment group** and **serum 25(OH)D** at 12 months
- BMI and age were not significant

To quantify the effect of vitamin D status on cancer risk, a simple logistic regression model was used:

$$\text{logit}(p) = \beta_0 + \beta_1 \cdot 25(\text{OH})\text{D}$$

Where:

- p is the probability of developing cancer
- 25(OH)D is the baseline serum vitamin D level (in nmol/L)
- β_1 reflects the change in log-odds of cancer per 1 nmol/L increase

The study reported a relative risk of cancer of 0.983 per 1 nmol/L increase in baseline serum 25(OH)D:

$$RR_1 = 0.983$$

To estimate the risk reduction for a 25 nmol/L increase, we raise the RR to the power of 25:

$$RR_{25} = 0.983^{25} \approx 0.65$$

Interpretation: An RR of approximately 0.65 means there is a **35% reduction in cancer risk** for every 25 nmol/L increase in serum 25(OH)D:

$$1 - 0.65 = 0.35 \quad \Rightarrow \quad 35\% \text{ reduced risk}$$

This supports the conclusion that higher vitamin D levels are significantly associated with lower cancer risk.

There were no serious adverse events linked to supplementation. Minor events, such as renal stones, occurred infrequently and were not significantly different between groups. The findings suggest that vitamin D, especially when combined with calcium, may offer a safe and effective strategy for reducing cancer risk in older women. These results support further research and consideration of vitamin D in public health policy related to cancer prevention.

Summary

- Calcium + Vitamin D supplementation significantly reduced the risk of non-skin cancer, especially after excluding cases from the first year (RR = 0.232, p-value = 0.005).
- Kaplan-Meier survival curves show improved cancer-free survival in the Ca + D group compared to placebo, indicating a protective effect over time.
- Both baseline and treatment-induced serum 25(OH)D concentrations were strong predictors of cancer risk.
- Raw data suggested a marginal protective effect for the Ca-only intervention, per-protocol analysis based on compliance did not improve the RR for the Ca-only group. Marginal calcium effect may represent a chance occurrence.

Bibliography

- [1] Joan M. Lappe, Dianne Travers-Gustafson, K. Michael Davies, Robert R. Recker, Robert P. Heaney *Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial*, The American Journal of Clinical Nutrition, June 2007, Volume 85, Issue 6, Pages 1586–1591.
<https://pubmed.ncbi.nlm.nih.gov/17556697/>
- [2] https://en.wikipedia.org/wiki/Relative_risk

Thank you for your
attention!