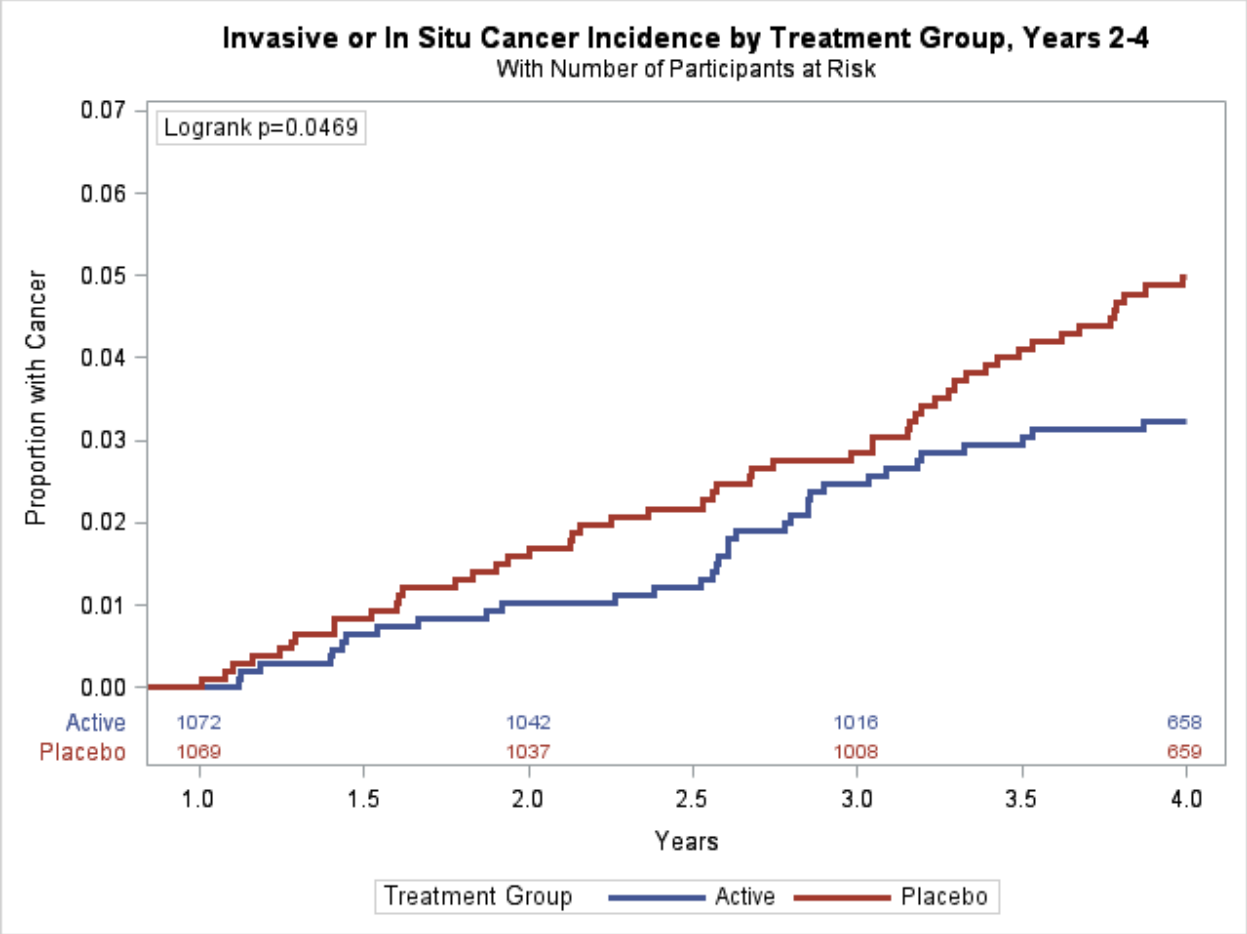
Supplementary Online Content

Lappe J, Watson P, Travers-Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.2115

This supplementary material has been provided by the authors to give readers additional information about their work.

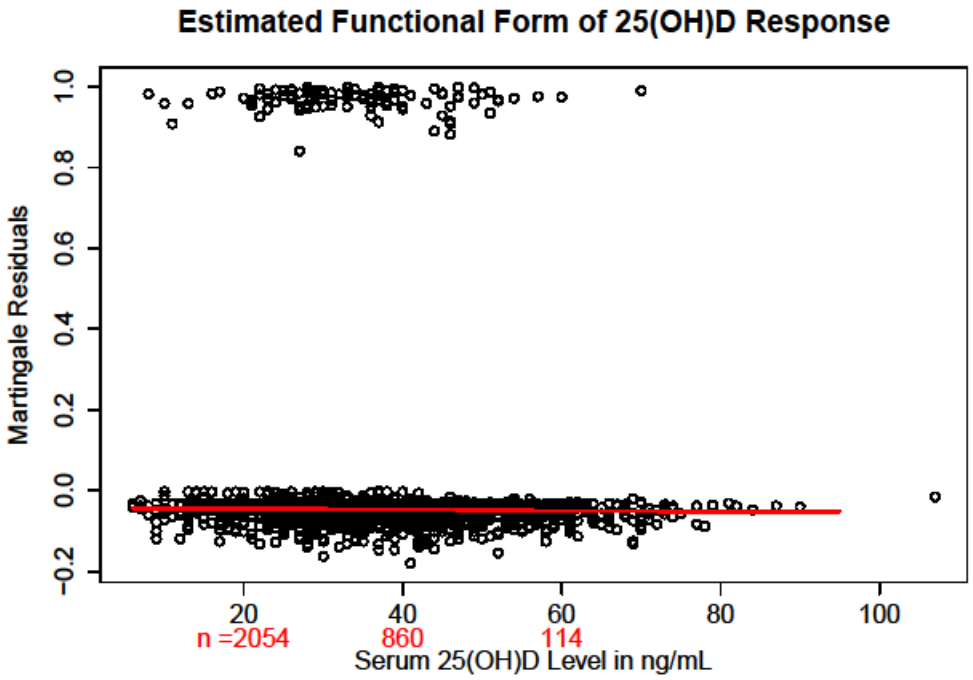
eFigure 1. *Post hoc* analysis Invasive and *in situ* Cancer-Free Kaplan-Meier Survival by Treatment Group Years 2-4



Post hoc analysis showing Kaplan-Meier invasive or *in situ* cancer incidence function by treatment group, including events during years 2-4 only. This figure excludes 84 participants in the treatment group and 78 participants in the placebo group who enrolled but then withdrew, or were diagnosed with an invasive or *in situ* cancer, prior to completing 1 year of follow-up. The median duration of follow-up was 4.0 years in both treatment groups. Numbers on study at each year are provided along the bottom of the figure. The probability associated with the log-rank test of equality over strata (logrank) is provided.

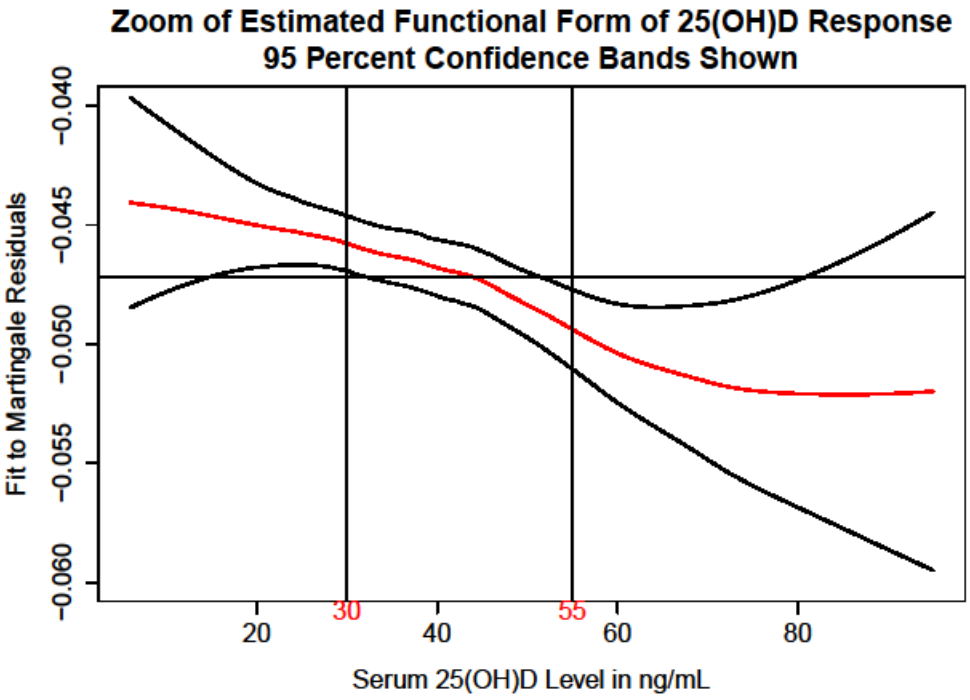
eFigure 2.

A. Estimated Functional Form of 25(OH)D Response.



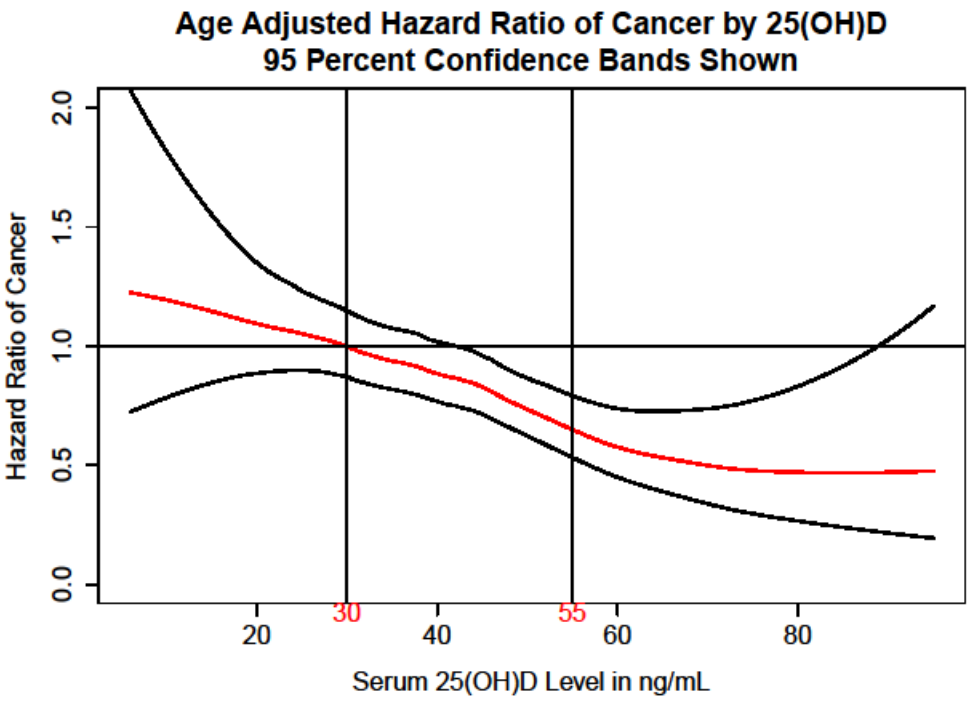
Martingale residuals from a Cox PH model using age alone plotted against 25(OH)D levels, with a loess smooth of the data to emphasize the trend superimposed. Serum levels range from 6 to 107 ng/mL, with the vast majority between 30 and 55.

B. Zoom of Estimated Functional Form of 25(OH)D Response 95 Percent Confidence Bands Shown



Zoom on the loess fit, with 95% confidence intervals from the loess function shown. The achieved 25(OH)D level was significantly inversely associated with cancer incidence (p=0.03, coef=-0.017). Compared with 25(OH)D level of 30 ng/ml as baseline, the estimated HR for cancer incidence for 25(OH)D levels between 30 and 55 ng/ml was 0.65 (CI, 0.44, 0.97).

C. Age Adjusted Hazard Ratio of Cancer by 25(OH)D 95 Percent Confidence Bands Shown.



Rescaled version of (2B) with y-axis values mapped to units of hazard ratios (HRs) for more direct interpretation.

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Statistical Analysis

Based on the previous study,[1] 25(OH)D levels were expected to be comparable between treatment groups, but to reach different steady state levels after a year or more of supplementation. In this study, 25(OH)D was treated as a time-varying covariate covering two discrete time intervals: from enrollment until the second 25(OH)D measurement at the end of year 1 of study, withdrawal, or cancer diagnosis, whichever came first, and from the second measurement until the end of follow up. Baseline 25(OH)D was used for the first interval, and 25(OH)D at the second measurement for the second interval.

Model checking for survival data involves examination of residuals (commonly used in regression models) adapted to allow for censoring; martingale residuals[2] (MRs) are one such adaptation. If the model fits well, there should be no clear structure in the MRs. If plots of MRs against values of a covariate not in the model show structure, the model could likely be improved by adding that covariate. MRs, which can range from 1 to –infinity and can be skewed, can show large gaps between values of uncensored (mostly positive) and censored observations (all negative), so data smoothers such as loess are often used to highlight structure.[3]

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Martingale residuals from an age-adjusted Cox model vs 25(OH)D levels are shown in Supplemental Figure 2A. The loess fit for the martingale residuals suggested linearity between 30 and 55 ng/mL (See Supplemental Figure 2B); slope changes beyond these points coincided with widening confidence bands, indicating inadequate data to draw conclusions. Supplemental Figure 2C shows the same curve after linearly rescaling the vertical axis y to map the level at 30 to 0, the level at 55 to the offset suggested by the Cox model, and exponentiating.

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1. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007;85(6):1586-1591.

2.Therneau T, Grambsch P, Fleming T. Martingale-based residuals for survival models. Biometrika. 1990;77:147-160.

3. Collett D. Modeling Survival Data in Medical 11 Research. New York: CRC Press; 2014.