Annals of Internal Medicine ORIGINAL RESEARCH

Long-Term Effect of Randomization to Calcium and Vitamin D Supplementation on Health in Older Women

Postintervention Follow-up of a Randomized Clinical Trial

Cynthia A. Thomson, PhD, RD; Aaron K. Aragaki, MS; Ross L. Prentice, PhD; Marcia L. Stefanick, PhD; JoAnn E. Manson, MD, MPH, DrPH; Jean Wactawski-Wende, PhD; Nelson B. Watts, MD; Linda Van Horn, PhD, RD; James M. Shikany, DrPH; Thomas E. Rohan, MBBS, PhD, DHSc; Dorothy S. Lane, MD, MPH; Robert A. Wild, MD, PhD, MPH; Rogelio Robles-Morales, MD; Aladdin H. Shadyab, PhD, MPH; Nazmus Saquib, MBBS, MPH, PhD, MBA; and Jane Cauley, DrPH

Background: Although calcium and vitamin D (CaD) supplementation may affect chronic disease in older women, evidence of long-term effects on health outcomes is limited.

Objective: To evaluate long-term health outcomes among postmenopausal women in the Women's Health Initiative CaD trial.

Design: Post hoc analysis of long-term postintervention follow-up of the 7-year randomized intervention trial of CaD. (ClinicalTrials.gov: NCT00000611)

Setting: A multicenter ($n = 40$) trial across the United States.

Participants: 36 282 postmenopausal women with no history of breast or colorectal cancer.

Intervention: Random 1:1 assignment to 1000 mg of calcium carbonate (400 mg of elemental calcium) with 400 IU of vitamin D_3 daily or placebo.

Measurements: Incidence of colorectal, invasive breast, and total cancer; disease-specific and all-cause mortality; total cardiovascular disease (CVD); and hip fracture by randomization assignment (through December 2020). Analyses were stratified on personal supplement use.

Results: For women randomly assigned to CaD versus placebo, a 7% reduction in cancer mortality was observed after a median cumulative follow-up of 22.3 years (1817 vs. 1943 deaths; hazard ratio [HR], 0.93 [95% CI, 0.87 to 0.99]), along with a 6% increase in CVD mortality (2621 vs. 2420 deaths; HR, 1.06 [CI, 1.01 to 1.12]). There was no overall effect on other measures, including all-cause mortality (7834 vs. 7748 deaths; HR, 1.00 [CI, 0.97 to 1.03]). Estimates for cancer incidence varied widely when stratified by whether participants reported supplement use before randomization, whereas estimates on mortality did not vary, except for CVD mortality.

Limitation: Hip fracture and CVD outcomes were available on only a subset of participants, and effects of calcium versus vitamin D versus joint supplementation could not be disentangled.

Conclusion: Calcium and vitamin D supplements seemed to reduce cancer mortality and increase CVD mortality after more than 20 years of follow-up among postmenopausal women, with no effect on all-cause mortality.

Primary Funding Source: National Heart, Lung, and Blood Institute of the National Institutes of Health.

Ann Intern Med. doi:10.7326/M23-2598 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 12 March 2024.

Evidence supports the role of adequate intake of calcium and vitamin D (CaD) in the health of older women (1–6), although not consistently (1, 5, 7–10), possibly due to variable sufficient intake among postmenopausal women (11). The Women's Health Initiative (WHI) completed the largest randomized controlled trial (RCT) of the effects of daily CaD supplementation (1000 mg of calcium [400 mg of elemental calcium] and 400 IU of vitamin D_3, taken in half doses twice daily) on health outcomes in postmenopausal women (12–14) (ClinicalTrials.gov: NCT00000611) and reported 7-year RCT results in 2006 (15, 16) with extended postintervention follow-up in 2013 (17). The results were largely null (18), although a 2009 report suggested lowered risk for cancer death among supplemented women (19) and a post hoc, subgroup analysis using a limited-access WHI data set reported that random assignment to CaD supplementation reduced incident total cancer, colorectal cancer (CRC), and invasive breast cancer, with no effect on total mortality, among women who were not taking CaD supplements before randomization (20).

The 20-year adjudication of health events and mortality in the WHI CaD RCT, complemented with National Death Index data (21), afforded an opportunity to evaluate longer-term health risks, especially for

See also:

Web-Only
Supplement

cancer and mortality in WHI. Further, we were able to evaluate for any differential effects of random assignment to CaD supplementation in relation to prior supplementation (vs. none), given that higher exposure or repletion of nutrients could protect against disease or death. The current analyses aimed to update the long-term findings of the WHI CaD trial and report findings stratified by history of personal supplementation before randomization, informed by pre- and postrandomization serum concentrations of vitamin D.

METHODS

Design Overview

This study is a post hoc analysis of long-term health outcomes in the WHI CaD RCT. The WHI included 4 clinical trials (CaD, diet modification, and hormone therapy [estrogen alone and estrogen plus progesterone]) as well as an observational trial (12). Women were invited to enroll in the CaD trial at the 1- and 2-year visits of the diet modification and hormone therapy trials; women could participate in 1 or more of the WHI clinical trials. Women taking calcium or vitamin D supplementation (or not) were eligible to participate in the CaD trial with no requirement to discontinue personal use of CaD during the trial.

Setting and Participants

The WHI CaD RCT was designed to test the effectiveness of CaD supplementation in reducing the incidence of bone fracture and CRC (12, 13). For the subgroup analysis, personal supplement use (none vs. any) included multivitamins (with or without minerals), other supplement mixtures (containing ≤10 vitamins or minerals, not including stress multisupplements), and single-supplement calcium or vitamin D. Supplement use was assessed by interviewer-administered supplement inventory (14) at trial screening and year 1 for eligibility for the CaD trial; again at years 3, 6, and 9; and again via self-report during the extended follow-up at 13.5 and 16.2 years (median). Main results were stratified by prerandomization supplement use, such that the group with no personal supplementation reported no use at both prerandomization visits (screening and year 1).

Randomization and Interventions

Eligible participants were assigned 1:1 via computer-generated, double-blind, random assignment with a concealed sequence to take 1000 mg of calcium carbonate (400 mg of elemental calcium) plus 400 IU (10 mcg) of vitamin D_3 (to be taken in half doses twice daily) or placebo (**Figure 1**). Personal supplemental calcium (up to 1000 mg/d) and vitamin D (up to 600 IU/d before 1999 and up to 1000 IU/d thereafter) were permitted. Study agent adherence was evaluated annually by pill count in the clinic. The trial was approved by institutional review boards at the 40 U.S.-based trial sites. The CaD trial randomly assigned 36 282 women who provided written informed consent to CaD supplementation (n = 18 176) or placebo (n = 18 106) for a median trial-specified intervention period of 7.0 years (IQR, 6.4 to 8.0 years).

Outcomes and Follow-up

Adjudicated Outcomes

Health status was documented among 93% of participants at CaD study closure (March 2005); 86.7% and 86.6% of surviving women consented to additional follow-up in extensions 1 and 2, respectively (**Figure 1**). Trial details, reported elsewhere (15–17), included prespecified outcomes adjudicated by centrally trained adjudicators along with 98% complete mortality data, complemented by National Death Index data through 31 December 2020 (21), over a cumulative median follow-up of 22.3 years (IQR, 18.0 to 23.5 years). Adjudicated cancer outcomes (CRC, invasive breast cancer, and total cancer) had a cumulative median follow-up of 20.9 years (IQR, 11.6 to 23.1 years). Hip fractures and cardiovascular disease (CVD) events (defined as myocardial infarction, coronary death, stroke, congestive heart failure, angina, peripheral vascular disease, carotid artery disease, coronary revascularization, and other cardiovascular death) were centrally adjudicated through 30 September 2010 and continued to be adjudicated for the hormone therapy trial and Black and Hispanic participants (Medical Records Cohort [MRC]; n = 11 492) (**Supplement Table**, available at Annals.org) (22). The overall cumulative median follow-up was 13.2 years (IQR, 11.3 to 19.6 years) for the full cohort in respect to monitoring and adjudication of CVD and hip fracture and 22.4 years (IQR, 20.5 to 23.5 years) for the MRC, where monitoring and adjudication occurred after 30 September 2010.

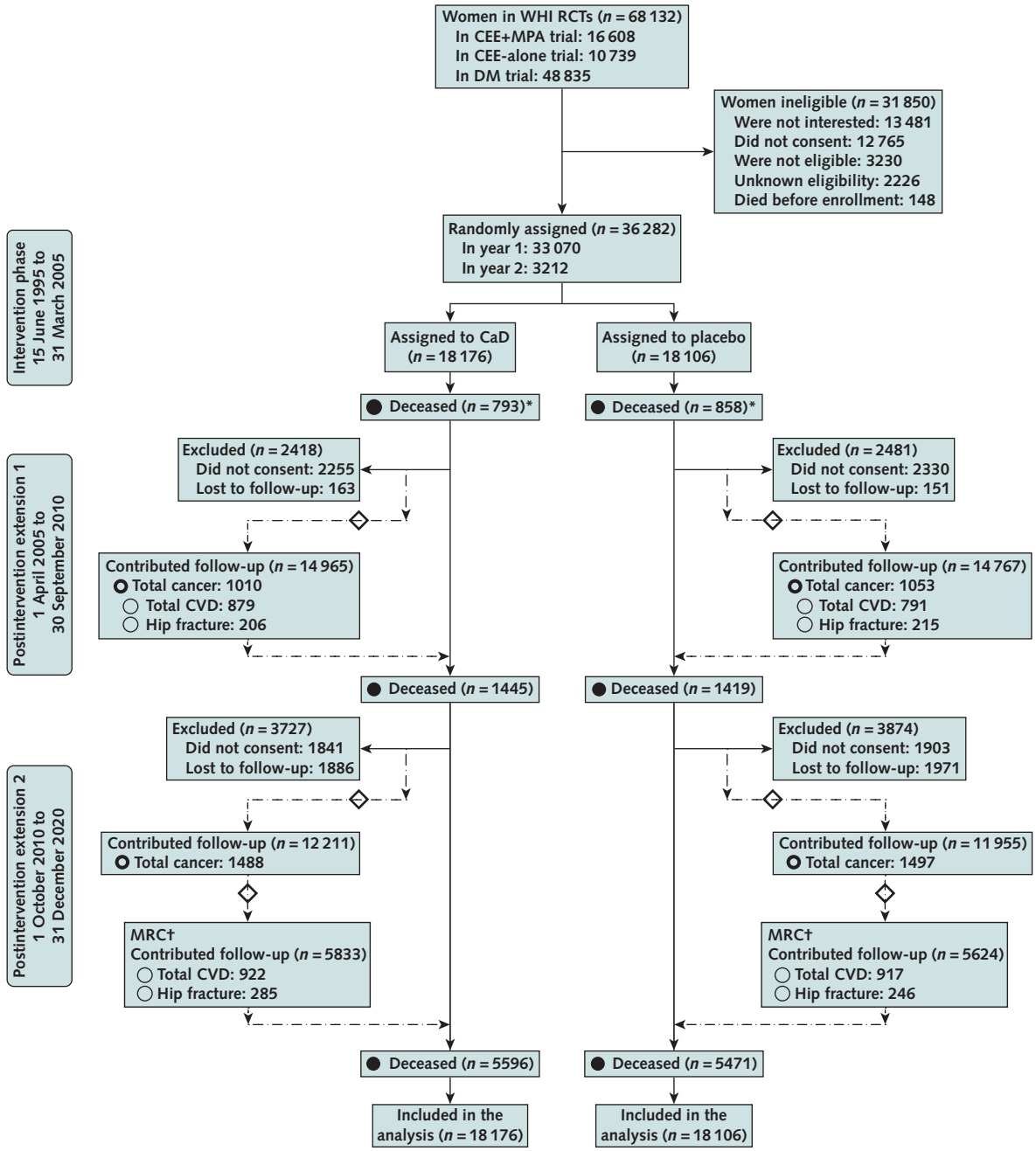
Serum 25-Hydroxyvitamin D

Standard protocols were used to collect, process, and store 12-hour fasting blood specimens at screening and year 1 for all clinical trial participants and at years 3, 6, and 9 for a random 6% subsample (14). A random, longitudinal subsample was selected for repeated measurements of serum 25-hydroxyvitamin D (25-(OH)D) concentration using the Diasorin LIAISON 25 OH Vitamin D TOTAL chemiluminescent immunoassay (23) to assess levels with the CaD intervention.

Demographic, Clinical, and Behavioral Characteristics

At study baseline, self-reported questionnaires obtained data for age, self-identified race and ethnicity, socioeconomic status, and education (14). Mammograms within the previous 12 months were evaluated along with self-reported cancer history to define women as cancer-free at enrollment. Clinic measures of height, weight, and waist circumference were taken. Health behaviors (diet, physical activity, and tobacco use) were measured using validated instruments.

Figure 1. Study flow diagram.



Solid circles indicate essentially complete mortality data; semisolid circles, adjudicated cancer outcomes available for the subset (*diamonds*) of participants who consented to extended follow-up; open circles, limited availability of other adjudicated outcomes for extension 2; only available for MRC (*diamonds*). CEE = conjugated equine estrogens; DM = low-fat dietary modification; CaD = calcium and vitamin D; CVD = cardiovascular disease; MPA = medroxyprogesterone acetate; MRC = Medical Records Cohort; RCT = randomized controlled trial; WHI = Women's Health Initiative.

* 763 vs. 821 deaths occurred before planned closeout; 30 vs. 37 deaths occurred after unblinding.

† The MRC included all former hormone trial participants and all non-Hispanic Black/African American and Hispanic/Latina participants (**Supplement Table**, available at Annals.org); 11 457 of 11 492 MRC participants contributed follow-up.

Statistical Analysis

Baseline characteristics were compared by randomization group and stratified by personal use of supplements before randomization. The primary analysis examined the overall influence of CaD assignment on colorectal, invasive breast, and total cancer incidence; disease-specific and all-cause mortality; total CVD; and hip fracture. Data were analyzed by CaD

assignment using time-to-event methods. Hazard ratios (HRs) were estimated using Cox regression models with baseline hazard functions stratified by age group at trial baseline (50 to 54, 55 to 59, 60 to 69, or 70 to 79 years), randomization status in the WHI hormone therapy and diet modification trials, history of disease (if applicable), and study period (study, extension 1, or extension 2; time-dependent). The time origin ($t = 0$) began at random assignment into the CaD trial (24). Participants contributed follow-up until trial closeout (31 December 2020 for cumulative follow-up), the date of their first clinical outcome, death, loss to follow-up, or the end of their follow-up consent period, whichever came first. Times to CVD outcomes and hip fracture were censored in 2010 for participants who were not part of the MRC (see Adjudicated Outcomes and **Figure 1**); corresponding analyses were inverse probability weighted to support valid estimation of HRs (with 95% CIs). Contrasts of CaD to placebo were based exclusively on follow-up accumulated after random assignment into the CaD trial. Incident events that occurred after the antecedent WHI trials began but before CaD randomization were excluded from CaD analyses (25). Selected results were investigated further with Kaplan–Meier curves, standardized using inverse probability weighting (26), and computed for the full cohort, so that personal supplement use and randomization groups were balanced with respect to age and other variables used to stratify the baseline hazard functions for the primary analysis. Kaplan–Meier estimates of 10-, 15-, and 20-year incidence rates were complemented by period-specific (biennial) HRs and cumulative HRs (with 95% CIs), computed under the proportional hazards assumption, using increasingly longer cumulative follow-up elapsed from randomization as additional temporal summaries of association (26). Adherence analyses, which censored participant follow-up 6 months after adherence dropped below 80% and weighted corresponding Cox models by the estimated inverse probability of adherence, complemented selected results (25).

Exploratory analyses parsed cancer mortality into CRC, invasive breast cancer, and total cancer deaths. The proportion of participants taking personal (nonstudy) supplements was longitudinally summarized with generalized estimating equations (27). Pre- and postrandomization concentrations of serum 25-(OH)D, stratified by randomization group and use of personal supplements before randomization, were plotted; geometric means (with 95% CIs) were weighted to align with the total proportions of participants who were randomly assigned. After peer review, *P* values were dropped from this report because significance was difficult to interpret for multiple comparisons of outcomes and because subgroup analysis was motivated by previous results in the same cohort; nominal 95% CIs should be interpreted cautiously. We used SAS software, version 9.4 (SAS Institute), and R software, version 4.0 (R Foundation for Statistical Computing; www.r-project.org; R packages survival and rmeta).

Role of the Funding Source

This analysis and the parent CaD supplementation trial were funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The National Heart, Lung, and Blood Institute reviewed the study design, monitored study conduct, and receives annual reports from study investigators. Representatives of the National Heart, Lung, and Blood Institute serve on the WHI steering committee, providing financial support and scientific insights to study operations.

RESULTS

Baseline characteristics were balanced between randomization groups (**Table**). Participants who reported prior supplement use (compared with those who did not) were older, more educated, and more often White; they had lower body mass index, higher self-reported physical activity, and lower tobacco use. Before randomization, median supplementation doses were 200 mg (IQR, 0 to 640 mg) for calcium and 375 IU (IQR, 0 to 400 IU) for vitamin D among women reporting supplementation (**Table**). In the 6% random subsample, prerandomization geometric mean concentrations of serum 25-(OH)D were 58.8 nmol/L (95% CI, 55.8 to 61.9 nmol/L) and 39.0 nmol/L (CI, 35.7 to 42.6 nmol/L) among participants who did and did not use personal supplements, respectively, with estimates weighted for the distribution of race and ethnicity.

During cumulative follow-up, randomization group was significantly associated with cancer and CVD mortality (**Figure 2**). Specifically, we found a 7% reduced risk for cancer death in favor of CaD (1817 deaths in the CaD group [annualized incidence, 0.50%] vs. 1943 in the placebo group [annualized incidence, 0.54%]; HR, 0.93 [CI, 0.87 to 0.99]) without evidence of a temporal association (**Supplement Figure 1**, *A*, available at Annals.org). Adherence analyses that censored participants who took fewer than 80% of study pills provided similar results (HR, 0.89 [CI, 0.80 to 0.99]). Exploratory analyses suggested no differential influence of CaD on cancer-specific mortality rates, including deaths from colorectal, breast, and other cancer. We found a 6% increased risk for CVD death (2621 deaths in the CaD group [annualized incidence, 0.72%] vs. 2420 in the placebo group [annualized incidence, 0.67%]; HR, 1.06 [CI, 1.01 to 1.12]) with evidence of a temporal association through extension 1 (**Supplement Figure 1**, *B*). Adherence analyses provided similar results (HR, 1.07 [CI, 0.97 to 1.18]). Randomization group was not associated with total CVD, but follow-up was available on only a subset during extension 2 (**Supplement Figure 2**, available at Annals.org). Randomization group was not associated with health outcomes during the intervention (**Supplement Figure 3**, available at Annals.org).

Table. Participant Characteristics in the WHI CaD Trial, by Randomization Group and Stratified by Personal Supplement Use Before Randomization ($n = 36\,282$)*

Characteristic	No Prior Supplement Use ($n = 11\,106$)		Prior Supplement Use ($n = 24\,651$)	
	CaD Supplementation ($n = 5621$)	Placebo ($n = 5485$)	CaD Supplementation ($n = 12\,274$)	Placebo ($n = 12\,377$)
Mean age (SD), *y*	61.6 (6.9)	61.6 (6.9)	62.8 (6.9)	62.7 (6.9)
Age group				
50–59 y	2413 (42.9)	2304 (42.0)	4196 (34.2)	4278 (34.6)
60–69 y	2359 (42.0)	2332 (42.5)	5793 (47.2)	5818 (47.0)
70–79 y	849 (15.1)	849 (15.5)	2285 (18.6)	2281 (18.4)
Hispanic/Latina†	335 (6.0)	332 (6.1)	501 (4.1)	471 (3.8)
Race†				
American Indian/Alaska Native	20 (0.4)	17 (0.3)	31 (0.3)	29 (0.2)
Asian/Pacific Islander	83 (1.5)	82 (1.5)	275 (2.2)	269 (2.2)
Black/African American	743 (13.2)	734 (13.4)	839 (6.8)	826 (6.7)
White	4580 (81.5)	4492 (81.9)	10 806 (88.0)	10 943 (88.4)
Multiracial, unknown, or not reported	195 (3.5)	160 (2.9)	323 (2.6)	310 (2.5)
College degree or higher	1875 (33.6)	1813 (33.2)	4602 (37.7)	4651 (37.8)
Median family income (IQR), *thousand $*	42.5 (27.5–62.5)	42.5 (27.5–62.5)	42.5 (27.5–62.5)	42.5 (27.5–62.5)
Smoking				
Never	2887 (51.8)	2842 (52.3)	6293 (51.8)	6461 (52.8)
Past	2126 (38.2)	2059 (37.9)	5024 (41.4)	4988 (40.7)
Current	555 (10.0)	531 (9.8)	826 (6.8)	796 (6.5)
Hysterectomy	2319 (41.3)	2419 (44.1)	5099 (41.5)	5040 (40.7)
Hormone replacement therapy use status				
Never used	3103 (55.3)	2972 (54.2)	5533 (45.1)	5538 (44.8)
Past user	1028 (18.3)	976 (17.8)	2160 (17.6)	2123 (17.2)
Current user	1485 (26.4)	1536 (28.0)	4571 (37.3)	4705 (38.0)
Self-reported health				
Excellent	974 (17.4)	933 (17.1)	2135 (17.5)	2145 (17.4)
Very good	2278 (40.8)	2218 (40.7)	5379 (44.0)	5435 (44.1)
Good	1896 (34.0)	1838 (33.7)	3968 (32.5)	4035 (32.7)
Fair/poor	435 (7.8)	465 (8.5)	730 (6.0)	709 (5.8)
Diabetes ever	373 (6.6)	393 (7.2)	659 (5.4)	628 (5.1)
History of cancer	209 (3.8)	227 (4.2)	519 (4.3)	460 (3.7)
Median body mass index (IQR), kg/m^2	28.9 (25.5–33.2)	28.9 (25.3–33.4)	27.8 (24.6–31.9)	27.7 (24.5–31.7)
Mean waist circumference (SD), *cm*	90.3 (13.8)	90.6 (13.9)	88.2 (13.6)	88.0 (13.5)
Mean Healthy Eating Index-2005 diet score (0 to 100 [best]) (SD)	63.0 (10.7)	62.9 (10.7)	65.6 (10.3)	65.7 (10.2)
Mean DASH diet score (8 to 40 [best]) (SD)	23.5 (4.7)	23.4 (4.7)	24.9 (4.6)	25.0 (4.5)
Median dietary calcium (IQR), *mg*	704 (482–1017)	717 (482–1022)	749 (525–1051)	750 (529–1054)
Median supplemental calcium (IQR), *mg*	0 (0–0)	0 (0–0)	200 (0–643)	200 (0–630)
Median calcium from medications (IQR), *mg*‡	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Median dietary vitamin D (IQR), *IU*	143 (92–216)	144 (93–220)	150 (97–223)	152 (98–222)
Median supplemental vitamin D (IQR), *IU*	0 (0–0)	0 (0–0)	400 (0–400)	343 (0–400)
Geometric mean serum 25-(OH)D level (geometric SD), *nmol/L*§	40.6 (2.1)	37.4 (1.8)	57.0 (1.6)	60.6 (1.7)
Mean systolic blood pressure (SD), *mm Hg*	127.7 (17.1)	128.5 (17.5)	127.2 (17.1)	127.1 (17.1)
Mean diastolic blood pressure (SD), *mm Hg*	76.4 (9.2)	76.6 (9.2)	75.6 (9.0)	75.6 (8.9)
Median physical functioning (0 to 100 [best]) (IQR)	90 (75–95)	90 (75–95)	90 (75–95)	90 (75–95)
Median episodes of moderate to strenuous physical activity per week (IQR), *n*	5.0 (0.5–12.7)	5.0 (0.5–13.0)	8.0 (2.3–17.0)	7.5 (2.3–17.1)
Personal (nonstudy) supplement use at follow-up				
Year 3	1362 (26.2)	1361 (26.9)	8932 (77.1)	9041 (77.4)
Year 6	2146 (43.1)	2095 (43.3)	8889 (80.5)	9088 (81.5)
Year 9	704 (54.7)	665 (55.3)	1780 (82.8)	1858 (83.8)

25-(OH)D = 25-hydroxyvitamin D; CaD = calcium and vitamin D.

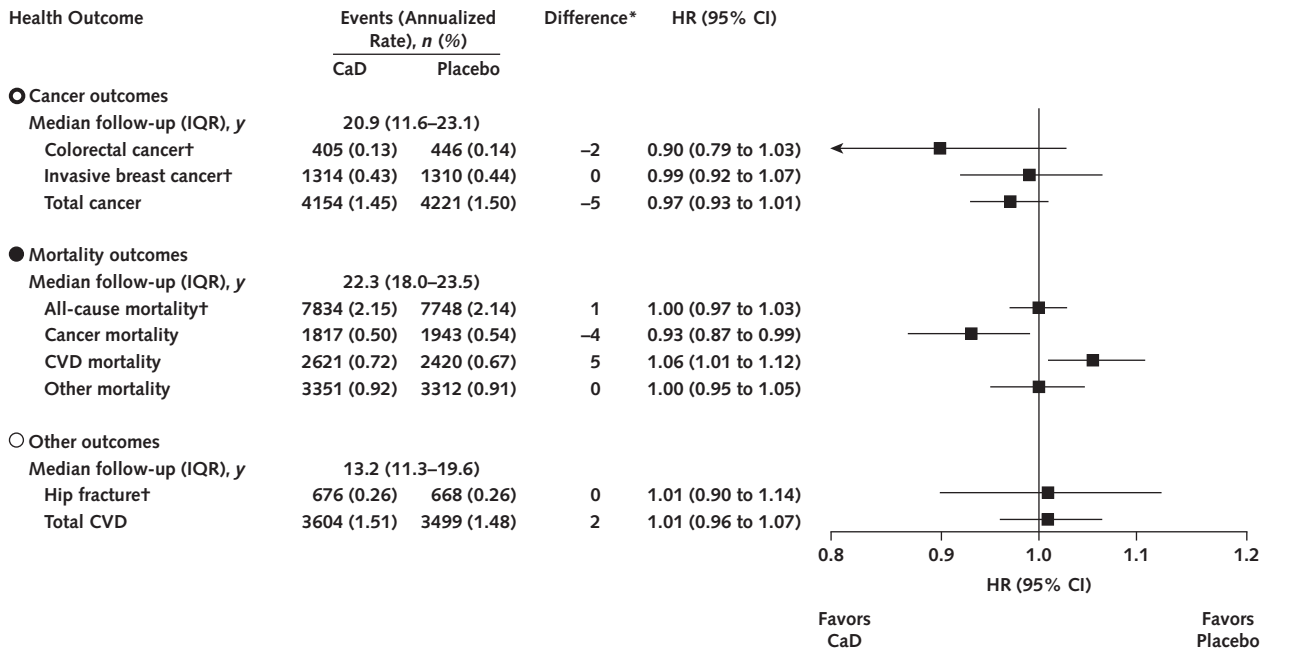
* Values are numbers (percentages) unless otherwise indicated. Characteristics were at screening except for personal supplement use during follow-up, reported at the bottom of the table. Personal supplement use indicates that the participant was taking a multivitamin (with or without minerals), other supplement mixture (mixture containing ≤10 vitamins or minerals, not including stress multisupplements), single-supplement calcium, or single-supplement vitamin D before randomization (WHI screening or 1 y later). 525 participants (1.4%) could not be stratified by personal supplement use before randomization: 354 were missing their 1-y inventory, and 171 were randomly assigned after the 1-y inventory.

† Ethnic group and race were self-reported by participants. Multiracial participants self-identified with more than 1 race. Participants of unknown race self-identified as other.

‡ Calcium carbonate from prescription and over-the-counter medications.

§ 6% random subsample of CaD trial participants, oversampled for minorities ($n = 296$ White; $n = 190$ Black; $n = 99$ Hispanic); $n = 114$ vs. 107 for participants with no prior supplement use, and $n = 177$ vs. 187 for participants with prior supplement use. Estimated geometric mean (geometric SD) were weighted to reflect distribution of race/ethnicity for the entire cohort.

Figure 2. Results for health outcomes in the overall study population of women aged 50–79 y in the WHI CaD trial during cumulative follow-up ($n = 36\,282$).



Solid circles indicate essentially complete mortality data; semisolid circles, adjudicated cancer outcomes available for participants who consented to extended follow-up; open circles, limited availability of other adjudicated outcomes for extension 2; see **Figure 1**. For other outcomes, Cox regression models used inverse probability weighting so summary statistics would represent the entire CaD trial. CaD = calcium and vitamin D; CVD = cardiovascular disease; HR = hazard ratio; IQR = interquartile range; WHI = Women's Health Initiative.

* Difference in estimated absolute risks (CaD − placebo) per 10 000 person-years.

† Monitored outcomes.

The proportion of participants taking personal supplements before randomization ranged from 55.2% (WHI baseline inventory) to 58.1% (WHI year 1 inventory) (**Supplement Figure 4**, *left*, available at Annals.org). Many women persistently either took ($n = 15\,856$) or did not take ($n = 11\,106$) personal supplements at the screening and year 1 prerandomization assessments, whereas 29.4% initiated and 18.7% ceased use between these visits (**Supplement Figure 4**, *right*). Personal supplement use was similar between groups during the intervention and follow-up. Among those with supplement use before randomization ($n = 24\,651$), daily personal (nonstudy) supplementation was 200 to 300 mg for calcium and 375 to 400 IU for vitamin D at screening or year 1 (**Supplement Figure 5**, available at Annals.org). After randomization, daily personal supplementation was mostly the same, with median intake of calcium and vitamin D near 0 for those with no prior use (**Supplement Figure 6**, available at Annals.org).

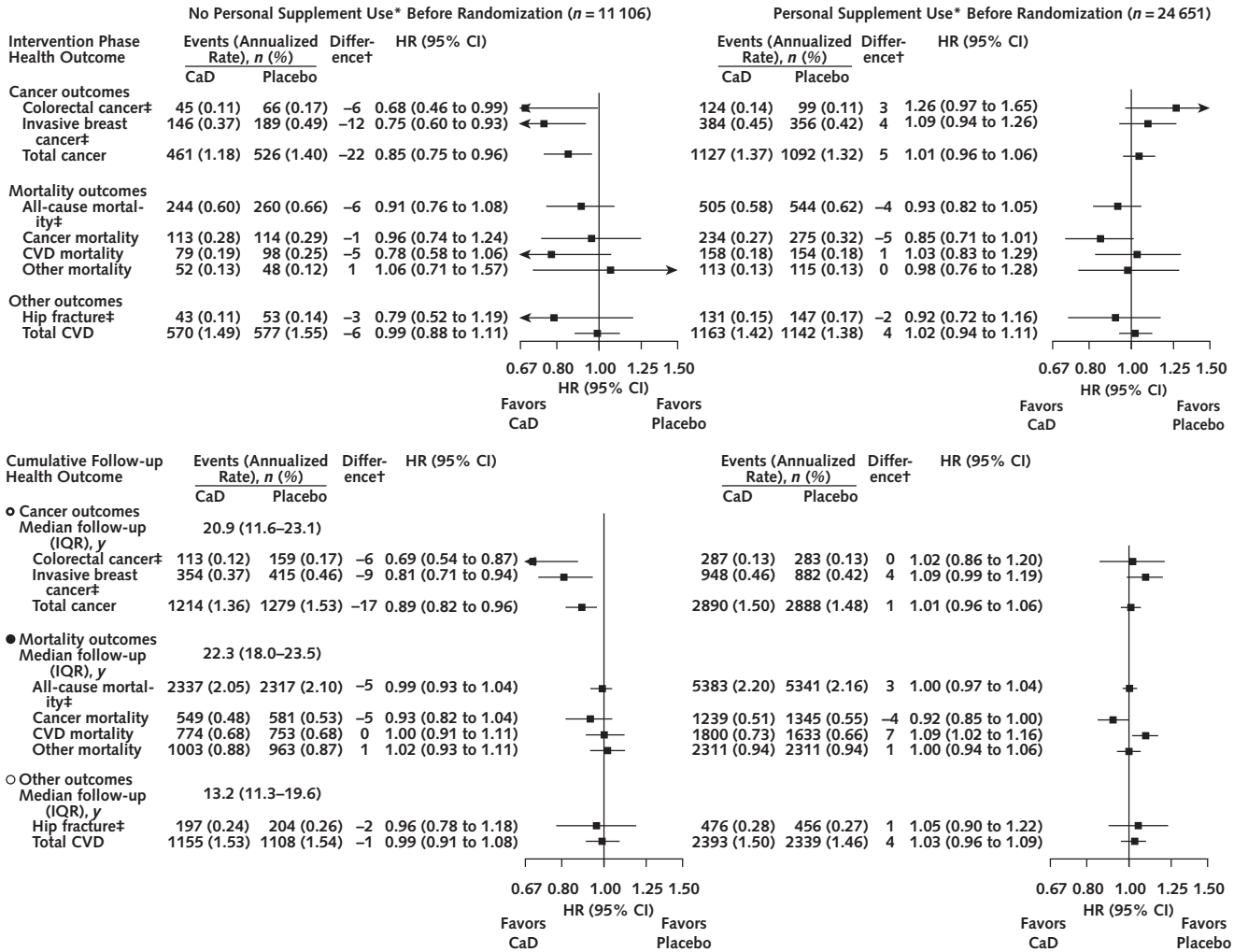
Stratification by prerandomization supplement use showed that during the intervention phase, women without supplement use (vs. those with) who had been randomly assigned to receive CaD had reductions in CRC (HR, 0.68 [CI, 0.46 to 0.99]), invasive breast cancer (HR, 0.75 [CI, 0.60 to 0.93]), and total cancer (HR, 0.85 [CI, 0.75 to 0.96]) (**Figure 3**, *top*). During this same period, there was no effect on CVD or mortality (total, cancer, or CVD-related). During cumulative follow-up, reductions in risk for CRC (HR, 0.69 [CI, 0.54 to 0.87]), invasive breast cancer (HR, 0.81 [CI, 0.71 to 0.94]), and total cancer (HR, 0.89 [CI, 0.82 to 0.96]) persisted (**Figure 3**, *bottom*; **Supplement Figures 7** to **9**, available at Annals.org), without a reduction in cancer mortality (HR, 0.93 [CI, 0.82 to 1.04]) (**Supplement Figure 10**, available at Annals.org). During cumulative follow-up, women reporting personal supplement use who had been randomly assigned to CaD (vs. placebo) had elevated CVD mortality (1800 vs. 1633 deaths; HR, 1.09 [CI, 1.02 to 1.16]), which was not evident in women not supplementing (**Supplement Figure 11**, available at Annals.org).

Baseline mean concentrations of serum 25-(OH)D showed means above the deficiency cut point of 50 nmol/L (28) (**Figure 4**) for women who used supplements and below that cut point for those who did not supplement. Two years later, 25-(OH)D concentrations were higher for women randomly assigned to CaD regardless of personal supplement use and were unchanged for the placebo group.

DISCUSSION

Analyses of long-term postintervention follow-up of the 7-year randomized intervention trial of CaD versus placebo suggest an overall 7% reduction in cancer mortality over the extended postintervention follow-up of more than 20 years combined. However, we

Figure 3. Results for health outcomes in the overall study population of women aged 50–79 y in the WHI CaD trial, stratified by personal (nonstudy) use of supplements before randomization (screening or 1-y visit), during the intervention and cumulative follow-up.



Solid circles indicate essentially complete mortality data; semisolid circles, adjudicated cancer outcomes available for participants who consented to extended follow-up; open circles, limited availability of other adjudicated outcomes for extension 2; see Figure 1. For other outcomes, Cox regression models used inverse probability weighting so summary statistics would represent the entire CaD trial. CaD = calcium and vitamin D; CVD = cardiovascular disease; HR = hazard ratio; IQR = interquartile range; WHI = Women's Health Initiative.

* Personal use of a multivitamin (with or without minerals), other supplement mixture (mixture containing ≤10 vitamins or minerals, not including stress multisupplements), single-supplement calcium, or single-supplement vitamin D before randomization.

† Difference in estimated absolute risks (CaD − placebo) per 10 000 person years.

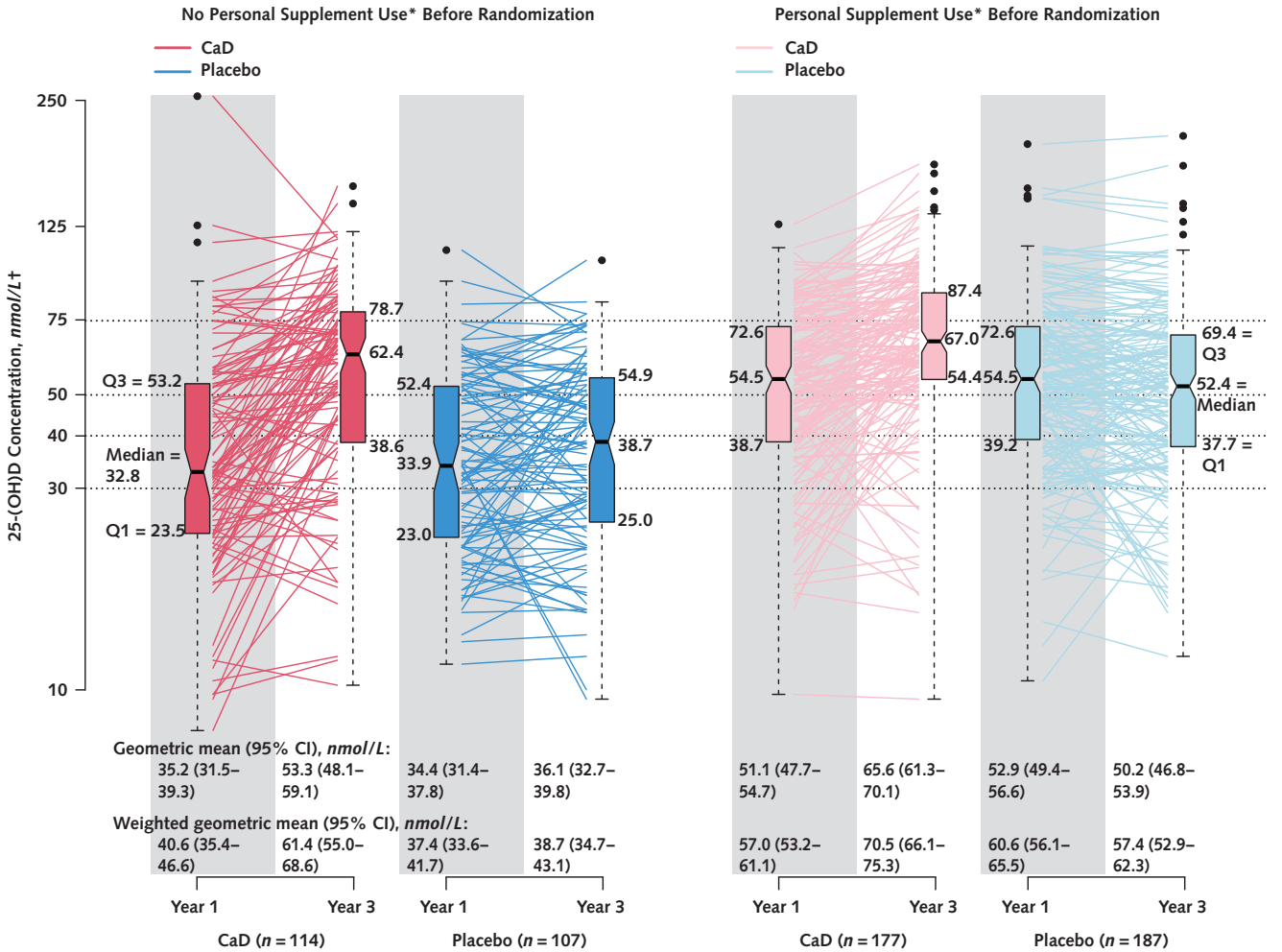
‡ Monitored outcomes.

also found 6% higher CVD mortality. No main effects on fracture, CVD, or cancer incidence or all-cause mortality were found.

In post hoc analyses stratified by use of supplementation before CaD randomization, our study also found an 11% lower risk for total cancer, including 31% and 19% lower incidences of CRC and invasive breast cancer, respectively, among participants without prior use; in contrast, point estimates for those reporting prior use exceeded 1, although 95% CIs were compatible with a negligible reduction to a modest increase in risk. Further, in contrast to no overall effect on CRC incidence reported in prior work (16), we found reduced CRC incidence (a protocol-designated secondary outcome) during the intervention phase in women without prerandomization supplementation. Nonetheless, CaD did not affect all-cause mortality regardless of prior supplementation status.

Given the multiple comparisons, our results should be interpreted with caution. Nevertheless, if real, the 7% reduction in longer-term cancer mortality would be clinically meaningful and is consistent with an earlier report of intervention phase outcomes (19). Available clinical trial evidence for the combination

Figure 4. Longitudinal serum 25-(OH)D concentrations in a subsample of women aged 50–79 y in the WHI CaD trial, before and 2 y after randomization, stratified by personal (nonstudy) use of supplements before randomization (screening or 1-y visit; $n = 585$).



Line plots connect each participant's 25-(OH)D concentrations and are summarized by corresponding box plots, where notches represent the approximate 95% CI for the median. Gray shading indicates measurements before randomization. Dotted reference lines indicate commonly used serum 25-(OH)D concentrations related to health. 25-(OH)D = 25-hydroxyvitamin D; CaD = calcium and vitamin D; Q = quartile; WHI = Women's Health Initiative.
* Personal use of a multivitamin (with or without minerals), other supplement mixture (mixture containing ≤10 vitamins or minerals, not including stress multisupplements), single-supplement calcium, or single-supplement vitamin D before randomization.
† To convert nmol/L to ng/mL, divide by 2.496.

of CaD in modifying cancer mortality beyond WHI is lacking, although evidence suggests that vitamin D without calcium supplementation may modify cancer mortality. In a recent meta-analysis of 5 RCTs, including the intervention phases of WHI and VITAL (Vitamin D and Omega-3 Trial) (29), vitamin D supplementation was associated with a significant overall reduction of 13% in cancer mortality (HR, 0.87 [CI, 0.79 to 0.96]) (30) that did not vary by attained 25-(OH)D levels. A recent secondary analysis of the VITAL randomized, placebo-controlled trial reported a 17% reduction for metastatic cancer and similar reductions in cancer mortality (31, 32).

Total cancer incidence was not reduced over the cumulative follow-up in our study (**Figure 2**), consistent with results at earlier time points (17). An RCT in 2303 older, healthy, postmenopausal women also found no effect on cancer incidence of supplementation with 1500 mg of calcium plus 2000 IU of vitamin D_3 over 4 years (33), nor did a meta-analysis by Keum and colleagues (30) of 10 supplementation trials evaluating vitamin D and cancer incidence.

Mechanistic support for CaD in cancer prevention exists, including decreases in tumor invasiveness and angiogenesis (34, 35); specific effects on bile acid, fatty acid metabolism, and gut uptake; and increased expression of protein kinase C (36). A 2015 review of vitamin D chemoprevention suggested numerous cancer protective mechanisms, including regulation of p21 tumor suppressor gene, modulation of proinflammatory

cytokines, activation of cyclin and cyclin-dependent kinases, regulation of forkhead box O (FoxO) proteins (37, 38), and reduced MIB-1 and increased p21 expression (38, 39).

Our findings that effects on cancer end points seem more prominent among those without prior CaD supplementation suggest that CaD supplementation may affect cancer biology primarily in the setting of augmenting an insufficiency in nutrient status. In support of this hypothesis, a large meta-analysis of 17 cohorts (40) concluded that low (<30 nmol/L) concentrations of 25-(OH)D, compared with sufficient concentrations, were associated with higher CRC risk. Of note, women not taking personal supplements in our sample had mean concentrations of serum 25-(OH)D below the 50-nmol/L threshold before randomization (41, 42) and exceeding the Institute of Medicine threshold after randomization to CaD (28). Our data suggest that higher concentrations of 25-(OH)D than are necessary for bone health (30 to 40 nmol/L) may be required to decrease cancer incidence (28, 34). Diets of older U.S. women have been shown to be low in CaD (11), as in our sample.

Although our findings align with prior work on vitamin D supplementation, findings on the effect of the CaD combination supplementation on CVD risk have been inconsistent (1, 43–45). We found no evidence of influence of CaD supplementation on CVD risk or CVD-specific mortality during the intervention period; however, a 6% time-varying elevation in CVD mortality was shown with longer follow-up. Mechanistic evidence suggests that calcium supplements may increase calcification of coronary arteries, thus increasing CVD mortality (46). Although 1 systematic review (47) found no altered risk for CVD with calcium with or without vitamin D (48), a meta-analysis suggested an 8% to 20% higher risk for coronary heart disease with calcium supplementation, with or without vitamin D (49). In contrast, vitamin D supplementation was not associated with CVD risk or mortality in another meta-analysis (10). The higher CVD mortality that emerged over longer follow-up, if attributable to CaD supplementation, suggests that calcium-induced coronary artery disease may manifest only after an extended period (50). An earlier WHI subset study showed no increase in coronary artery calcium in the CaD group, versus placebo, at the end of the CaD trial (51).

The strengths of this research are the large sample size, long-term follow-up, characterization of supplement use before and during the trial (to reduce measurement error) (52), adjudicated outcomes, and nearly complete mortality data. Longitudinal concentrations of serum 25-(OH)D informed subgroup analyses, because 25-(OH)D concentrations were below 50 nmol/L for those not using supplements before randomization.

However, important limitations should be noted, including this study's post hoc analysis and limited follow-up on total CVD and hip fracture. Further, some observations may be by chance given the multiple comparisons. Women reporting no supplementation differed from supplemented women on several demographic and health behavior characteristics, so the differential influence of CaD on cancer could be attributable partially to these characteristics and not solely to personal supplement use (53). In evaluations of clinical decisions for use, CaD supplementation in our sample did result in higher kidney stone risk (13). Findings may not be widely generalizable given the sample of more highly educated, predominantly non-Hispanic White, postmenopausal women.

Overall, these analyses suggest the possibility of a delayed effect of CaD supplementation in reducing cancer mortality among postmenopausal women, as well as the possibility of an increase in CVD mortality with no net effect on all-cause mortality. Effects of vitamin D supplementation for cancer prevention may depend on achieving serum vitamin D concentrations above 50 nmol/L. Given the study design, we could not disentangle the added benefit or harms of supplementation with CaD in combination versus vitamin D alone, a topic worthy of future study.

From Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona (C.A.T.); Fred Hutchinson Cancer Center, Seattle, Washington (A.K.A., R.L.P.); Department of Medicine, Stanford School of Medicine, Stanford University, Palo Alto, California (M.L.S.); Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (J.E.M.); School of Public Health and Health Professions, University at Buffalo, Buffalo, New York (J.W.); Jewish Hospital Mercy Health, Cincinnati, Ohio (N.B.W.); Feinberg School of Medicine, Northwestern University, Chicago, Illinois (L.V.H.); Division of Preventive Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama (J.M.S.); Albert Einstein College of Medicine, Bronx, New York (T.E.R.); Renaissance School of Medicine, Stony Brook, New York (D.S.L.); Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma (R.A.W.); Department of Clinical Translational Sciences, College of Medicine, University of Arizona, Tucson, Arizona (R.R.); Herbert Wertheim School of Public Health, University of California, San Diego, San Diego, California (A.H.S.); Clinical Sciences Department, College of Medicine, Sulaiman Alrajhi University, Al Bukayriyah, Saudi Arabia (N.S.); and University of Pittsburgh, Pittsburgh, Pennsylvania (J.C.).

Note: The full trial protocol and consent forms are available at www.whi.org/protocols-and-study-consents.

Financial Support: The WHI program is funded by the National Heart, Lung, and Blood Institute (National Institutes of Health, U.S. Department of Health and Human Services) through contracts 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, and 75N92021D00005.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-2598.

Data Sharing Statement: The following data will be made available with publication: deidentified participant data (www.whi.org/doc/WHI-Data-Sharing-Statement.pdf). The following supporting documents will be made available with publication: informed consent form (available through the WHI online resource, www.whi.org/datasets, while the WHI remains funded and indefinitely through the Biologic Specimen and Data Repository Information Coordinating Center [BioLINCC], https://biolincc.nhlbi.nih.gov/studies/whi_ctos). Eligible researchers with an approved specified purpose may download the data directly at the WHI online resource. Other researchers may download the data directly through BioLINCC, in accordance with the National Heart, Lung, and Blood Institute's BioLINCC guidelines.

Corresponding Author: Cynthia A. Thomson, PhD, RD, Professor, Health Promotion Sciences, Mel and Enid Zuckerman College of Public Health, University of Arizona, 3950 South Country Club Road, Suite 330, Tucson, AZ 85714; e-mail, cthomson@arizona.edu.

Author contributions are available at Annals.org.

References

1. **Yang B, Campbell PT, Gapstur SM, et al.** Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr. 2016;103:886-894. [PMID: 26864361] doi:10.3945/ajcn.115.117994
2. **Voutsadakis IA.** Vitamin D baseline levels at diagnosis of breast cancer: a systematic review and meta-analysis. Hematol Oncol Stem Cell Ther. 2021;14:16-26. [PMID: 33002425] doi:10.1016/j.hemonc.2020.08.005
3. **Uusi-Rasi K, Kärkkäinen MUM, Lamberg-Allardt CJE.** Calcium intake in health maintenance - a systematic review. Food Nutr Res. 2013;57. [PMID: 23687486] doi:10.3402/fnr.v57i0.21082
4. **Rautiainen S, Sesso HD, Manson JE.** Large-scale randomized clinical trials of bioactives and nutrients in relation to human health and disease prevention - lessons from the VITAL and COSMOS trials. Mol Aspects Med. 2018;61:12-17. [PMID: 29222066] doi:10.1016/j.mam.2017.12.001
5. **Grandi NC, Breitling LP, Brenner H.** Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Prev Med. 2010;51:228-233. [PMID: 20600257] doi:10.1016/j.ypmed.2010.06.013
6. **Ford JA, MacLennan GS, Avenell A, et al; RECORD Trial Group.** Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr. 2014;100:746-755. [PMID: 25057156] doi:10.3945/ajcn.113.082602
7. **Carroll C, Cooper K, Papaioannou D, et al.** Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clin Ther. 2010;32:789-803. [PMID: 20685491] doi:10.1016/j.clinthera.2010.04.024
8. **Weingarten MA, Zalmanovici A, Yaphe J.** Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev. 2008;2008:CD003548. [PMID: 18254022] doi:10.1002/14651858.CD003548.pub4
9. **Sperati F, Vici P, Maugeri-Saccà M, et al.** Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. PLoS One. 2013;8:e69269. [PMID: 23894438] doi:10.1371/journal.pone.0069269
10. **Barbarawi M, Kheiri B, Zayed Y, et al.** Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol. 2019;4:765-776. [PMID: 31215980] doi:10.1001/jamacardio.2019.1870
11. **Bailey RL, Dodd KW, Goldman JA, et al.** Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr. 2010;140:817-822. [PMID: 20181782] doi:10.3945/jn.109.118539
12. **The Women's Health Initiative Study Group.** Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials. 1998;19:61-109. [PMID: 9492970] doi:10.1016/s0197-2456(97)00078-0
13. **Jackson RD, LaCroix AZ, Cauley JA, et al.** The Women's Health Initiative calcium-vitamin D trial: overview and baseline characteristics of participants. Ann Epidemiol. 2003;13:S98-S106. [PMID: 14575942] doi:10.1016/s1047-2797(03)00046-2
14. **Anderson GL, Manson J, Wallace R, et al.** Implementation of the Women's Health Initiative study design. Ann Epidemiol. 2003;13:S5-S17. [PMID: 14575938] doi:10.1016/s1047-2797(03)00043-7
15. **Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators.** Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354:669-683. [PMID: 16481635] doi:10.1056/NEJMoa055218
16. **Wactawski-Wende J, Kotchen JM, Anderson GL, et al; Women's Health Initiative Investigators.** Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354:684-696. [PMID: 16481636] doi:10.1056/NEJMoa055222
17. **Cauley JA, Chlebowski RT, Wactawski-Wende J, et al.** Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt). 2013;22:915-929. [PMID: 24131320] doi:10.1089/jwh.2013.4270
18. **Prentice RL, Pettinger MB, Jackson RD, et al.** Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013;24:567-580. [PMID: 23208074] doi:10.1007/s00198-012-2224-2
19. **LaCroix AZ, Kotchen J, Anderson G, et al.** Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2009;64:559-567. [PMID: 19221190] doi:10.1093/gerona/glp006
20. **Bolland MJ, Grey A, Gamble GD, et al.** Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. Am J Clin Nutr. 2011;94:1144-1149. [PMID: 21880848] doi:10.3945/ajcn.111.015032
21. **Rich-Edwards JW, Corsano KA, Stampfer MJ.** Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol. 1994;140:1016-1019. [PMID: 7985649] doi:10.1093/oxfordjournals.aje.a117191
22. **Anderson GL, Burns CJ, Larsen J, et al.** Use of administrative data to increase the practicality of clinical trials: insights from the Women's Health Initiative. Clin Trials. 2016;13:519-526. [PMID: 27365013] doi:10.1177/1740774516656579
23. Liaison 25 OH Vitamin D Total Assay. Diasorin. 2021. Accessed at https://int.diasorin.com/en/immunodiagnostics/metabolic-disorders/vitamin-d on 5 January 2024.
24. **Kalbfleisch JD, Prentice RL.** The Statistical Analysis of Failure Time Data. 2nd ed. J Wiley; 2011.
25. **Robins JM, Finkelstein DM.** Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics. 2000;56:779-788. [PMID: 10985216] doi:10.1111/j.0006-341x.2000.00779.x
26. **Hernán MA.** The hazards of hazard ratios. Epidemiology. 2010;21:13-15. [PMID: 20010207] doi:10.1097/EDE.0b013e3181c1ea43
27. **Fitzmaurice GM, Laird NM, Ware JH.** Applied Longitudinal Analysis. 2nd ed. J Wiley; 2012.
28. **Ross AC, Manson JE, Abrams SA, et al.** The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96:53-58. [PMID: 21118827] doi:10.1210/jc.2010-2704

29. **Manson JE, Cook NR, Lee IM, et al; VITAL Research Group.** Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019;380:33-44. [PMID: 30415629] doi:10.1056/NEJMoa1809944
30. **Keum N, Lee DH, Greenwood DC, et al.** Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Ann Oncol. 2019;30:733-743. [PMID: 30796437] doi:10.1093/annonc/mdz059
31. **Chandler PD, Chen WY, Ajala ON, et al; VITAL Research Group.** Effect of vitamin D_3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. JAMA Netw Open. 2020;3:e2025850. [PMID: 33206192] doi:10.1001/jamanetworkopen.2020.25850
32. **Zhang Y, Fang F, Tang J, et al.** Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ. 2019;366:l4673. [PMID: 31405892] doi:10.1136/bmj.l4673
33. **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. 2017;317:1234-1243. [PMID: 28350929] doi:10.1001/jama.2017.2115
34. **Feldman D, Krishnan AV, Swami S, et al.** The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. 2014;14:342-357. [PMID: 24705652] doi:10.1038/nrc3691
35. **Deeb KK, Trump DL, Johnson CS.** Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007;7:684-700. [PMID: 17721433] doi:10.1038/nrc2196
36. **Lamprecht SA, Lipkin M.** Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. Nat Rev Cancer. 2003;3:601-614. [PMID: 12894248] doi:10.1038/nrc1144
37. **Giammanco M, Di Majo D, La Guardia M, et al.** Vitamin D in cancer chemoprevention. Pharm Biol. 2015;53:1399-1434. [PMID: 25856702] doi:10.3109/13880209.2014.988274
38. **Gao Y, Um CY, Fedirko V, et al.** Effects of supplemental vitamin D and calcium on markers of proliferation, differentiation, and apoptosis in the normal colorectal mucosa of colorectal adenoma patients. PLoS One. 2018;13:e0208762. [PMID: 30557404] doi:10.1371/journal.pone.0208762
39. **LeBoff MS, Chou SH, Ratliff KA, et al.** Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med. 2022;387:299-309. [PMID: 35939577] doi:10.1056/NEJMoa2202106
40. **McCullough ML, Zoltick ES, Weinstein SJ, et al.** Circulating vitamin D and colorectal cancer risk: an international pooling project of 17 cohorts. J Natl Cancer Inst. 2019;111:158-169. [PMID: 29912394] doi:10.1093/jnci/djy087
41. **LeFevre ML; U.S. Preventive Services Task Force.** Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;162:133-140. [PMID: 25419853] doi:10.7326/M14-2450
42. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al; Endocrine Society.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-1930. [PMID: 21646368] doi:10.1210/jc.2011-0385
43. **Michaëlsson K, Melhus H, Warensjö Lemming E, et al.** Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346:f228. [PMID: 23403980] doi:10.1136/bmj.f228
44. **Avenell A, Gillespie WJ, Gillespie LD, et al.** Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009;:CD000227. [PMID: 19370554] doi:10.1002/14651858.CD000227.pub3
45. **Chan R, Leung J, Woo J.** A prospective cohort study examining the associations of dietary calcium intake with all-cause and cardiovascular mortality in older Chinese community-dwelling people. PLoS One. 2013;8:e80895. [PMID: 24224062] doi:10.1371/journal.pone.0080895
46. **Tankeu AT, Ndip Agbor V, Noubiap JJ.** Calcium supplementation and cardiovascular risk: a rising concern. J Clin Hypertens (Greenwich). 2017;19:640-646. [PMID: 28466573] doi:10.1111/jch.13010
47. **Chung M, Tang AM, Fu Z, et al.** Calcium intake and cardiovascular disease risk: an updated systematic review and meta-analysis. Ann Intern Med. 2016;165:856-866. [PMID: 27776363] doi:10.7326/M16-1165
48. **Asemi Z, Saneei P, Sabihi SS, et al.** Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: a meta-analysis of observational studies. Nutr Metab Cardiovasc Dis. 2015;25:623-634. [PMID: 25912278] doi:10.1016/j.numecd.2015.03.008
49. **Yang C, Shi X, Xia H, et al.** The evidence and controversy between dietary calcium intake and calcium supplementation and the risk of cardiovascular disease: a systematic review and meta-analysis of cohort studies and randomized controlled trials. J Am Coll Nutr. 2020;39:352-370. [PMID: 31625814] doi:10.1080/07315724.2019.1649219
50. **Anderson JJ, Kruszka B, Delaney JA, et al.** Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 2016;5:e003815. [PMID: 27729333] doi:10.1161/JAHA.116.003815
51. **Manson JE, Allison MA, Carr JJ, et al; Women's Health Initiative and Women's Health Initiative-Coronary Artery Calcium Study Investigators.** Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010;17:683-691. [PMID: 20551849] doi:10.1097/gme.0b013e3181d683b5
52. **Patterson RE, Levy L, Tinker LF, et al.** Evaluation of a simplified vitamin supplement inventory developed for the Women's Health Initiative. Public Health Nutr. 1999;2:273-276. [PMID: 10512561] doi:10.1017/s1368980099000361
53. **VanderWeele TJ, Knol MJ.** Interpretation of subgroup analyses in randomized trials: heterogeneity versus secondary interventions. Ann Intern Med. 2011;154:680-683. [PMID: 21576536] doi:10.7326/0003-4819-154-10-201105170-00008

Author Contributions: Conception and design: A.K. Aragaki, J. E. Manson, R.L. Prentice, M.L. Stefanick, C.A. Thomson, L. Van Horn, N.B. Watts.
Analysis and interpretation of the data: A.K. Aragaki, J.E. Manson, R.L. Prentice, A.H. Shadyab, M.L. Stefanick, L. Van Horn, N.B. Watts, R.A. Wild.
Drafting of the article: A.K. Aragaki, C.A. Thomson, L. Van Horn.
Critical revision for important intellectual content: A.K. Aragaki, J. Cauley, D.S. Lane, J.M. Shikany, J.E. Manson, R.L. Prentice, R. Robles-Morales, T.E. Rohan, N. Saquib, A.H. Shadyab, M.L. Stefanick, L. Van Horn, J. Wactawski-Wende, R.A. Wild.
Final approval of the article: A.K. Aragaki, J. Cauley, D.S. Lane, J.M. Shikany, J.E. Manson, R.L. Prentice, R. Robles-Morales, T.E. Rohan, N. Saquib, A.H. Shadyab, M.L. Stefanick, C.A. Thomson, L. Van Horn, J. Wactawski-Wende, N.B. Watts, R.A. Wild.
Provision of study materials or patients: D.S. Lane, L. Van Horn, J. Wactawski-Wende, N.B. Watts.
Statistical expertise: A.K. Aragaki, R.L. Prentice, N. Saquib.
Obtaining of funding: R.L. Prentice, J. Wactawski-Wende.
Administrative, technical, or logistic support: J. Cauley, C.A. Thomson, L. Van Horn, J. Wactawski-Wende.
Collection and assembly of data: A.K. Aragaki, J. Cauley, J.E. Manson, R.L. Prentice, M.L. Stefanick, L. Van Horn, J. Wactawski-Wende, N.B. Watts.