Vitamin D With or Without Calcium Supplementation for Prevention of Cancer and Fractures: An Updated Meta-analysis for the U.S. Preventive Services Task Force

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Background: Studies suggest that vitamin D supplementation may reduce cancer and fracture risks.

Purpose: To examine the benefits and harms of vitamin D with or without calcium supplementation on clinical outcomes of cancer and fractures in adults.

Data Sources: English-language studies identified from MEDLINE and the Cochrane Central Register of Controlled Trials through July 2011.

Study Selection: Randomized, controlled trials (RCTs), prospective cohort studies, and nested case–control studies reporting incidence of or death from cancer and fracture outcomes.

Data Extraction: Multiple reviewers extracted details about participant characteristics, including baseline vitamin D status and use of supplements; details of statistical analyses, including adjustments for confounding; and methodological quality. Differences were resolved by consensus.

Data Synthesis: 19 RCTs (3 for cancer and 16 for fracture outcomes) and 28 observational studies (for cancer outcomes) were analyzed. Limited data from RCTs suggested that high-dose (1000 IU/d) vitamin D supplementation can reduce the risk for total cancer, and data from observational studies suggested that higher blood 25-hydroxyvitamin D (25-[OH]D) concentrations might be associated with increased risk for cancer. Mixed-effects dose–response meta-analyses showed that each 10-nmol/L increase in blood 25-(OH)D concentration was associated with a 6% (95% CI, 3% to 9%) reduced risk for colorectal cancer but no statistically significant dose–response relationships for prostate and breast cancer. Random-effects model meta-analysis showed that combined vitamin D and calcium supplementation reduced fracture risk (pooled relative risk, 0.88 [CI, 0.78 to 0.99]) in older adults, but the effects differed according to study setting: institution (relative risk, 0.71 [CI, 0.57 to 0.89]) versus community-dwelling (relative risk, 0.89 [CI, 0.76 to 1.04]). One RCT showed adverse outcomes associated with supplementation, including increased risk for renal and urinary tract stones.

Limitations: Most trial participants were older (aged ≥65 years) postmenopausal women. Observational studies were heterogeneous and were limited by potential confounders.

Conclusion: Combined vitamin D and calcium supplementation can reduce fracture risk, but the effects may be smaller among community-dwelling older adults than among institutionalized elderly persons. Appropriate dose and dosing regimens, however, require further study. Evidence is not sufficiently robust to draw conclusions regarding the benefits or harms of vitamin D supplementation for the prevention of cancer.

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Editor's Note: The related draft recommendation statement will soon be available for public comment at www.uspreventiveservicestaskforce.org. The USPSTF will consider all submitted comments when it finalizes its recommendation. To sign up for notification about the posting of draft recommendation statements, please visit the USPSTF Web site.

One of the major biological functions of vitamin D is to regulate bone mineralization. Many tissues besides bone are also influenced by vitamin D (1). There are 2 forms of vitamin D: D_3 (cholecalciferol) and D_2 (ergocalciferol). Both forms are biologically activated in humans by hydroxylation first in the liver, to form 25-hydroxyvitamin D (25-[OH]D), and subsequently in the kidneys, to form 1,25-dihydroxyvitamin D (1,25-[OH]$_2$D). Although 25-(OH)D has low biological activity, it is the major form of vitamin D that circulates in the bloodstream. Thus, blood 25-(OH)D concentrations are generally thought to reflect nutritional status regarding vitamin D (2, 3). In addition to indirectly affecting bone mineralization, 1,25-(OH)$_2$D has further, diverse biological effects. For example, as recently noted, 1,25-(OH)$_2$D inhibits parathyroid hormone secretion and promotes insulin secretion, inhibits adaptive immunity and promotes innate immunity, and inhibits proliferation and stimulates differentiation of cells (4). These functions suggest a possible role of vitamin D in cancer prevention.

This review is based in part on our 2009 evidence report (5) on the relationship of vitamin D and calcium, with 17 health outcomes, that was produced to inform an

Context

People want to know about potential benefits and harms of vitamin D supplementation.

Contribution

This review of 19 trials and 28 observational studies reports the following: Combined vitamin D and calcium supplementation reduce fracture risk in older persons; optimum dosing regimens are unclear; effects of vitamin D supplementation on cancer risk are uncertain; and supplementation may increase the risk for renal and urinary tract stones.

Caution

Most trials involved older women. Observational studies were limited by confounding factors.

Implication

Vitamin D supplementation can reduce fracture risk, but optimal doses and effects on cancer risk are uncertain.

—*The Editors*

Institute of Medicine committee charged to update the Dietary Reference Intakes for vitamin D and calcium (6). Here, we updated and reanalyzed part of our broad systematic review to support the U.S. Preventive Services Task Force (USPSTF) recommendations on vitamin D with or without calcium supplements for preventing cancer and fractures. Following USPSTF methods (7), we used an analytic framework (**Appendix Figure 1**, available at www.annals.org) that maps the 4 key questions (KQs) evaluated in the current review: KQ 1 addresses the effects of vitamin D supplementation on cancer and fracture outcomes, KQ 2 addresses the associations between vitamin D status and cancer and fracture outcomes, KQ 3 addresses the effects of vitamin D supplementation on changes in vitamin D status, and KQ 4 addresses the adverse events associated with supplementation (see **Table 1** for full KQs).

METHODS

Our 2009 evidence report on vitamin D and calcium (5) included a systematic review of primary studies for cancer outcomes and updated a previous systematic review by the University of Ottawa Evidence-based Practice Center on fractures, published in 2007 (8). In the current review, we present a focused update of these 2 systematic reviews (5, 8).

Data Sources and Searches

In our 2009 evidence report, we searched MEDLINE and the Cochrane Central Register of Controlled Trials through April 2009 for primary studies of any design. Search terms included *vitamin D*, *25-hydroxyvitamin D*, *calcium*, and text terms and Medical Subject Heading terms related to cancer or neoplasms, fracture, and bone mineral density. We limited searches to articles about human participants published in English-language journals. The complete search strategies have been published elsewhere (5). We updated specific searches for cancer and fracture outcomes through July 2011.

Study Selection and Outcomes of Interest

For cancer, clinical outcomes of interest included incidence of or death from prostate, colorectal, or breast cancer or from all types of cancer combined (total cancer). For fractures, clinical outcomes of interest included incidence of any fracture at any site (for example, hip, spine, or wrist). We recorded whether the cancer or fracture outcomes were primary or secondary end points in the original article.

For benefits and harms of vitamin D supplementation (KQs 1 and 4), we included randomized, controlled trials (RCTs) of generally healthy adults (<20% of study participants had major chronic diseases, such as diabetes or cardiovascular disease, at baseline) that compared vitamin D supplementation with or without calcium against no supplementation or placebo for the outcomes of interest. For the purpose of our review, we excluded studies that enrolled pregnant women only or measured vitamin D status only during pregnancy and RCTs comparing different dosages of vitamin D supplementation without a control group that did not receive vitamin D supplementation. To include available data on elderly persons (aged ≥65 years), we also accepted RCTs of older ambulatory adults with any disease other than cancer. We excluded short-term (<1 month) RCTs and trials that used synthetic vitamin D analogues (for example, oxacalcitriol or paricalcitol).

For associations between vitamin D status and outcomes (KQ 2), we included prospective cohort or nested case–control studies of adults that investigated the associations of vitamin D status (as measured by blood 25-[OH]D) with cancer outcomes of interest. In contrast to cancer outcomes, for which only a limited number of RCTs were eligible, a large number of RCTs reporting fracture outcomes met our eligibility criteria; therefore, we decided not to update the observational studies of the associations of vitamin D status and fracture outcomes, instead referring to the Ottawa evidence report (which is current up to 2005) (8) for this question.

For effects of vitamin D supplementation on changes in vitamin D status (KQ 3), we adopted the results from our 2009 evidence report (5) and did not update the search.

Data Extraction and Quality Assessment

For all eligible RCTs and observational studies in the present update, we extracted data on study characteristics, participant characteristics, details on vitamin D and calcium supplements, baseline vitamin D status (including assay used, definition of outcomes, and study results). For RCTs, the number of events and total number of participants in each group were extracted to calculate effect sizes.

Table 1. **Key Questions and Summary of Evidence Reviewed**

KQs and Comparisons of Interest	Outcomes	Studies (Total Sample Size)	Methodologic Quality	Follow-up Duration	Main Findings	Supplement or Appendix Figure Providing Details
KQ 1: What are the effects of vitamin D with or without calcium supplements on the clinical outcomes of cancer and fractures in RCTs? (overarching question)						
Vitamin D supplementation vs. placebo*	Total cancer	2 RCTs (*n* = 3577)	2 fair	4–5 y	1 RCT in elderly men and women, aged ≥71 y (*n* = 2686) Incidence: HR, 1.09 (95% CI, 0.86–1.36) Mortality: HR, 0.86 (CI, 0.61–1.20) 1 RCT in postmenopausal women, aged >55 y (*n* = 891)† Incidence: RR, 0.76 (CI, 0.86–1.55) Mortality: RR, 0.55 (CI, 0.24–1.28)	Supplement 1
	Colorectal cancer	1 RCT (*n* = 2686)	1 fair	5 y	Incidence: HR, 1.02 (CI, 0.60–1.74) Mortality: HR, 0.62 (CI, 0.24–1.60)	Supplement 1
	Breast cancer	1 RCT (*n* = 2686)	1 fair	5 y	Incidence: HR, 0.99 (CI, 0.25–4.0) Mortality: NR	Supplement 1
	Fracture	5 RCTs (*n* = 14 583)	1 good 3 fair 1 poor	7 mo–5 y	Meta-analysis of 5 RCTs in elderly men and women (*n* = 14 583) Overall: RR, 1.03 (CI, 0.84–1.26) Institutionalized: RR, 0.99 (CI, 0.72–1.34) Community-dwelling: RR, 1.06 (CI, 0.77–1.46)	Supplement 2
Combined vitamin D and calcium supplementation vs. placebo	Total cancer	2 RCTs (*n* = 37 016)	1 good 1 fair	4–7 y	1 RCT in postmenopausal women, aged >55 y (*n* = 734)† Incidence: RR, 0.40 (CI, 0.20–0.82)‡ Mortality: RR, 0.23 (CI, 0.09–0.60)‡ 1 RCT in postmenopausal women (*n* = 36 282) Incidence: HR, 0.98 (CI, 0.91–1.05) Mortality: HR, 0.89 (CI, 0.77–1.03)	Supplement 1
	Colorectal cancer	1 RCT (*n* = 36 282)	1 good	7 y	Incidence: HR, 1.08 (CI, 0.86–1.34) Mortality: HR, 0.82 (CI, 0.52–1.29)	Supplement 1
	Breast cancer	1 RCT (*n* = 36 282)	1 good	7 y	Incidence: HR, 0.96 (CI, 0.86–1.07) Mortality: HR, 0.99 (CI, 0.55–1.76)	Supplement 1
	Fracture	11 RCTs (*n* = 52 915)	2 good 5 fair 4 poor	1–7 y	Meta-analysis of 11 RCTs in mostly (69%) postmenopausal women (*n* = 52 915) Overall: RR, 0.88 (CI, 0.79–0.99)‡ Institutionalized: RR, 0.71 (CI, 0.57–0.89)‡ Community-dwelling: RR, 0.89 (CI, 0.76–1.04) Community-dwelling with history of fracture: RR, 1.02 (CI, 0.89–1.16)	Supplement 2
KQ 2: What are the associations between vitamin D status and the clinical outcomes of cancer and fractures in observational studies?						
Dose–response relationship between 25-(OH)D concentration at baseline and risk for cancer	Total cancer	3 prospective cohort studies (*n* = 19 503)	1 good 2 fair	Mean, 7–14 y	Higher 25-(OH)D concentrations were associated with increased risk for total cancer mortality in men, but the ranges of 25-(OH)D concentrations varied across studies One study found that baseline blood 25-(OH)D concentration was not associated with risk for total cancer mortality in adult women (*n* = 8914)	Supplement 3; Supplement 4
	Colorectal cancer	9 nested case–control studies (3136 cases)	8 fair 1 poor	NA	Linear dose–response meta-analysis of 9 studies Pooled adjusted OR, 0.94 (CI, 0.91–0.97)‡ per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3
	Prostate cancer	11 nested case–control studies (4005 cases)	4 fair 7 poor	NA	Linear dose–response meta-analysis of 8 studies Pooled adjusted OR, 1.01 (CI, 0.99–1.04) per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3

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Table 1—Continued

KQs and Comparisons of Interest	Outcomes	Studies (Total Sample Size)	Methodologic Quality	Follow-up Duration	Main Findings	Supplement or Appendix Figure Providing Details
	Breast cancer	5 nested case–control studies (3128 cases)	3 fair 2 poor	NA	Linear dose–response meta-analysis of 4 studies Pooled adjusted OR, 0.99 (CI, 0.97–1.01) per 10-nmol/L increase in 25-(OH)D concentration	Supplement 3
	Fracture	15 studies (3 prospective cohorts and 12 case–control studies) were reviewed in the University of Ottawa Evidence-based Practice Center evidence report (8)			Overall, there is inconsistent evidence for an association between serum 25-(OH)D concentrations and the risk for fractures. One of 3 cohorts reported an inverse association between blood 25-(OH)D concentrations and fracture rates, and 9 of 12 case–control studies found significantly lower 25-(OH)D concentrations in cases vs. controls.	
KQ 3: What are the effects of vitamin D with or without calcium supplements on the net changes in vitamin D status in RCTs?						
Dose of vitamin D supplement	Net changes in blood 25-(OH)D concentration	26 RCTs included in our 2009 evidence report (5)			Clear relationship between increasing dose of vitamin D_3 and increasing net change in blood 25-(OH)D concentration	Appendix Figure 7
KQ 4: What are the adverse outcomes associated with vitamin D and calcium supplements in RCTs?						
Vitamin D with or without calcium supplementation vs. placebo	Adverse events	All 63 RCTs included in our 2009 evidence report (5) and 19 RCTs included in the focused update			The majority of RCTs did not provide information on adverse events and were not adequately powered to detect adverse events. 1 RCT in postmenopausal women (*n* = 36 282) Renal stones: HR, 1.17 (CI, 1.02–1.34) Urinary tract stones: HR, 1.17 (CI, 1.02–1.34)	

25-(OH)D = 25-hydroxyvitamin D; HR = hazard ratio; KQ = key question; NA = not applicable; NR = not reported; OR = odds ratio; RCT = randomized, controlled trial; RR = risk ratio.
* We considered the comparison of combined vitamin D and calcium supplementation vs. calcium supplementation alone to be equivalent to vitamin D supplementation vs. placebo.
† Sample size is specific to the comparison. This 3-group RCT enrolled a total of 1179 postmenopausal women.
‡ Statistically significant ($P < 0.05$).

For observational studies, we selected the results from the full statistical model that adjusted for the largest number of potential confounders and recorded the number of cases and total number at risk (for cohort studies) or controls (for nested case–control studies) for each blood 25-(OH)D category, if reported. All quantitative data were verified by a second reviewer. For observational studies, we also listed the confounders adjusted for in the study design (for example, matching factors) or analyses.

We used the Agency for Healthcare Research and Quality Methods Reference Guide for Effectiveness Reviews criteria to grade study methodologic quality as good, fair, or poor (9). For RCTs, we applied quality items described in the CONSORT (Consolidated Standards of Reporting Trials) statement (10). For observational studies, we applied quality items described in the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement (11), and specific items concern-

ing the background vitamin D exposure, adjustment for potential confounding factors, and clarity of reporting of vitamin D status assessments and statistical analyses. For each included study, 1 reviewer rated study quality, which was confirmed by at least 1 other reviewer. Disagreements were resolved by consensus.

Data Synthesis

For analyses of RCTs included for KQ 1, we used the DerSimonian–Laird random-effects model meta-analysis (12) to examine the effects of vitamin D with or without calcium supplements on fractures. Most of these studies reported more than 1 fracture outcome. We selected 1 fracture outcome from each study to be included in our meta-analyses based on the descending order of most reported outcomes: total fracture, hip fracture, and nonvertebral fracture. We tested for heterogeneity with the Cochran *Q* statistic (considered significant when the *P* value was

less than 0.10) and quantified the extent of heterogeneity with the I^2 index. We defined low, moderate, and high heterogeneity as I^2 values of 25%, 50%, and 75%, respectively. These cutoffs are arbitrary and were used for descriptive purposes only (13).

We reported the effects of combined vitamin D and calcium supplementation separately from vitamin D supplementation alone on cancer and fracture outcomes. Subgroup analyses were performed to evaluate the influences of study populations (that is, institutionalized or community-dwelling adults) on the pooled effect estimates. The Z test was used to test the difference in estimates of pooled effects between subgroups. We also used random-effects meta-regression (fitted with restricted maximum likelihood) (14, 15) to explore whether the effects of vitamin D supplementation on fracture outcomes depends on 2 factors: daily dose of vitamin D supplementation and baseline blood 25-(OH)D concentration.

For the analyses of observational studies included for KQ 2, we performed mixed-effects logistic regression to assess the dose–response relationships of blood 25-(OH)D concentrations with colorectal, prostate, and breast cancer risks by using adjusted results from full multivariable models (see the **Appendix**, available at www.annals.org, for details).

Analyses were conducted by using Stata SE 11 software (StataCorp, College Station, Texas). All P values were 2-tailed, and a P value less than 0.05 was considered to indicate a significant difference, unless otherwise specified.

Role of the Funding Source

The Agency for Healthcare Research and Quality funded this focused update under a contract to support the USPSTF. The funding source had no role in study selection, quality assessment, or data synthesis, although they provided project oversight and reviewed the draft evidence synthesis.

RESULTS
Search Results

We included 137 studies in this review: 19 RCTs for KQ 1 (3 for cancer outcomes and 16 for fracture outcomes), 28 observational studies and 1 systematic review for KQ 2, 26 RCTs for KQ 3, and 63 RCTs for KQ 4. **Appendix Figure 2** (available at www.annals.org) shows the summary results from evidence searches and study selection. **Table 1** provides an overview of the numbers of studies and participants, methodological quality, and main findings of the included studies.

Effects of Vitamin D, With or Without Calcium, on Cancer and Fracture Outcomes
Cancer

Three RCTs reported effects of vitamin D with or without calcium supplements on clinical cancer outcomes (**Supplement 1**, available at www.annals.org). Cancer outcomes were secondary end points in all 3 RCTs. Of these,

2 RCTs (16, 17) were rated as fair quality because of a high rate of loss to follow-up (>10%) or unclear reporting of randomization and allocation concealment. The third RCT (18, 19) was rated as good quality (**Appendix Figure 3**, available at www.annals.org). Although all 3 RCTs enrolled older adults, they focused on distinct populations: Two enrolled generally healthy postmenopausal women, and 1 enrolled elderly men and women (aged ≥71 years). These RCTs lasted 4 to 7 years and were heterogeneous in the dose and regimen of vitamin D_3 supplementation. The results from these 3 RCTs are summarized in **Table 1**. Of note, 1 RCT (16) provided data for 2 comparisons: vitamin D supplementation versus placebo and combined vitamin D and calcium supplementation versus placebo.
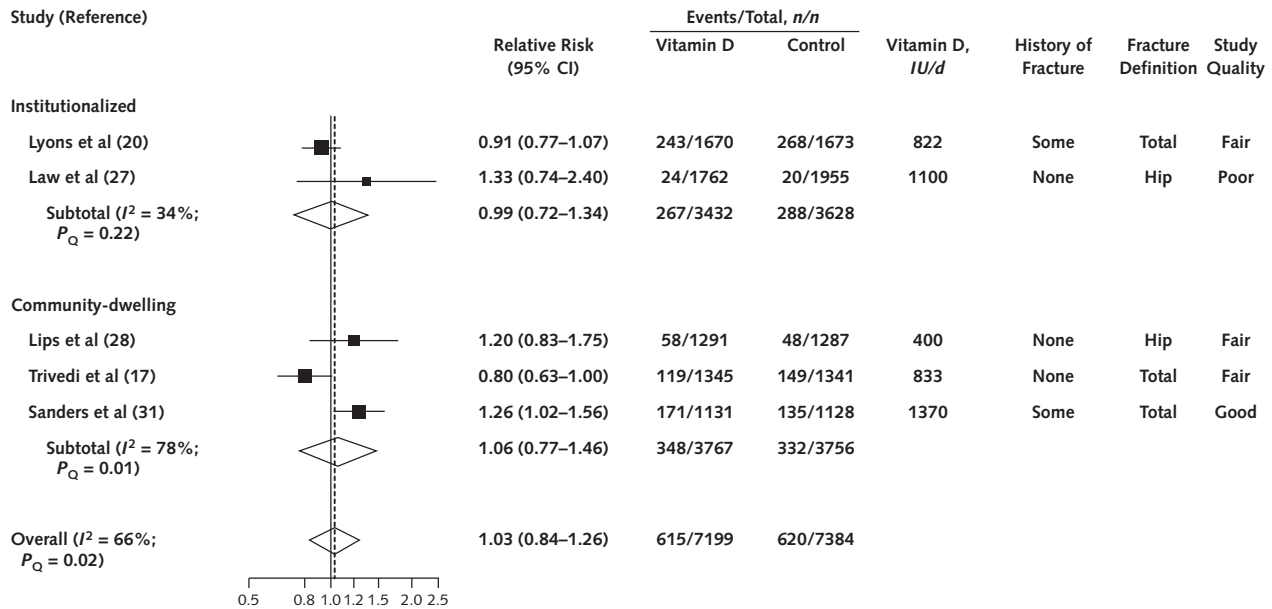
Vitamin D Supplementation Versus Placebo. Two fair-quality RCTs contributed information to this comparison (16, 17). Dose and regimen of vitamin D_3 supplementation were 100 000 IU every 4 months in the trial conducted in the United Kingdom (17) and 1100 IU daily in the trial conducted in Nebraska (16). A total of 2686 elderly men and women and 891 healthy postmenopausal women were evaluated. The hazard or risk ratios for the incidence and mortality of colorectal, breast, or total cancer ranged from 0.55 to 1.09 (<1.0 favors vitamin D_3 supplementation), with wide CIs (**Table 1**). On the basis of the CIs, one cannot rule out the possibility of clinically important effects in risk in either direction (for example, a protective effect of at least 14% reduction in risk or a harmful effect of at least 20% increase in risk).

Combined Vitamin D and Calcium Supplementation Versus Placebo. Two RCTs (1 of good quality [18, 19] and 1 of fair quality [16]) enrolled a total of 37 016 postmenopausal women, 98% of whom were from the Women's Health Initiative trial (18, 19). Daily dose and regimen of vitamin D_3 (plus calcium) supplementation were 400 IU (plus 1500 mg) in the Women's Health Initiative trial (18, 19) and 1100 IU (plus 1400 to 1500 mg) in the trial in Nebraska (16). The Women's Health Initiative trial showed hazard ratios of total cancer or any specific cancer (including colorectal and breast) ranging from 0.96 to 1.08, with narrow CIs, for cancer incidence (18, 19). In contrast, the smaller trial conducted in Nebraska reported a 60% (CI, 18% to 80%) reduction in the risk for total cancer incidence (**Table 1**) (16).

Fracture

Sixteen RCTs (17, 20–34) examined the effects of vitamin D with or without calcium supplements on fracture outcomes (**Supplement 2**, available at www.annals.org). Of these, 3 RCTs were of good quality, 7 were of fair quality, and 4 were of poor quality (**Appendix Figure 4**, available at www.annals.org). Fracture outcomes were primary end points in 13 (81%) of the 16 RCTs. Eight of the RCTs reported an outcome of fracture at any site, 5 reported data on hip fracture, 2 reported nonvertebral fracture, and 1 did not define the fracture outcome.

Figure 1. Results of random-effects meta-analysis of the effects of vitamin D supplementation compared with placebo on total fracture in randomized, controlled trials.

Study (Reference)	Relative Risk (95% CI)	Events/Total, *n/n* Vitamin D	Events/Total, *n/n* Control	Vitamin D, IU/d	History of Fracture	Fracture Definition	Study Quality
Institutionalized							
Lyons et al (20)	0.91 (0.77–1.07)	243/1670	268/1673	822	Some	Total	Fair
Law et al (27)	1.33 (0.74–2.40)	24/1762	20/1955	1100	None	Hip	Poor
Subtotal (I^2 = 34%; P_Q = 0.22)	0.99 (0.72–1.34)	267/3432	288/3628				
Community-dwelling							
Lips et al (28)	1.20 (0.83–1.75)	58/1291	48/1287	400	None	Hip	Fair
Trivedi et al (17)	0.80 (0.63–1.00)	119/1345	149/1341	833	None	Total	Fair
Sanders et al (31)	1.26 (1.02–1.56)	171/1131	135/1128	1370	Some	Total	Good
Subtotal (I^2 = 78%; P_Q = 0.01)	1.06 (0.77–1.46)	348/3767	332/3756				
Overall (I^2 = 66%; P_Q = 0.02)	1.03 (0.84–1.26)	615/7199	620/7384				

Vitamin D Supplementation Versus Placebo. Five RCTs compared supplemental vitamin D (400 to 1370 IU/d) with placebo in a total of 14 583 elderly men and women (17, 20, 27, 28, 31), with follow-up ranging from 7 months to 5 years. Of these, 1 RCT was of good quality, 3 were of fair quality, and 1 was of poor quality. Common limitations among the fair- or poor-quality RCTs were unclear reporting of randomization and outcome assessment and lack of allocation concealment. The overall random-effects meta-analysis found that vitamin D supplementation alone did not reduce fracture risk (pooled relative risk, 1.03 [CI, 0.84 to 1.26]), with high heterogeneity across studies (I^2 = 60%; P = 0.02). The subgroup meta-analysis results according to setting (that is, institution vs. community) were similar to the overall effect estimate (**Figure 1**).

Combined Vitamin D and Calcium Supplementation Versus Placebo. Eleven RCTs compared the combination of vitamin D (300 to 1000 IU/d) and calcium (500 to 1200 mg/d) supplementation with placebo in a total of 52 915 persons (21–26, 29, 30, 32–34), mostly (69%) postmenopausal women from the Women's Health Initiative trial (33). Of these, 2 RCTs were of good quality, 5 were of fair quality, and 4 were of poor quality. Common limitations among the fair- or poor-quality RCTs were a high rate of loss to follow-up (>10%) and unclear reporting of randomization, allocation concealment, and outcome assessment. Follow-up ranged from 1 to 7 years among these RCTs.

Our random-effects meta-analysis showed that combined vitamin D and calcium supplementation reduced the risk for total fracture as compared with placebo (pooled relative risk, 0.88 [CI, 0.78 to 0.99]), with moderate heterogeneity across studies (I^2 = 36%; P = 0.11). Subgroup meta-analysis results showed that the pooled effect estimates differed according to setting (P = 0.07): There was a significant risk reduction among institutionalized elderly persons (relative risk, 0.71 [CI, 0.57 to 0.89]). The risk reduction was smaller in community-dwelling elderly persons or postmenopausal women (relative risk, 0.89 [CI, 0.76 to 1.04]) and no risk reduction among community-dwelling women with history of fracture (relative risk, 1.02 [CI, 0.89 to 1.16]) (**Figure 2**).
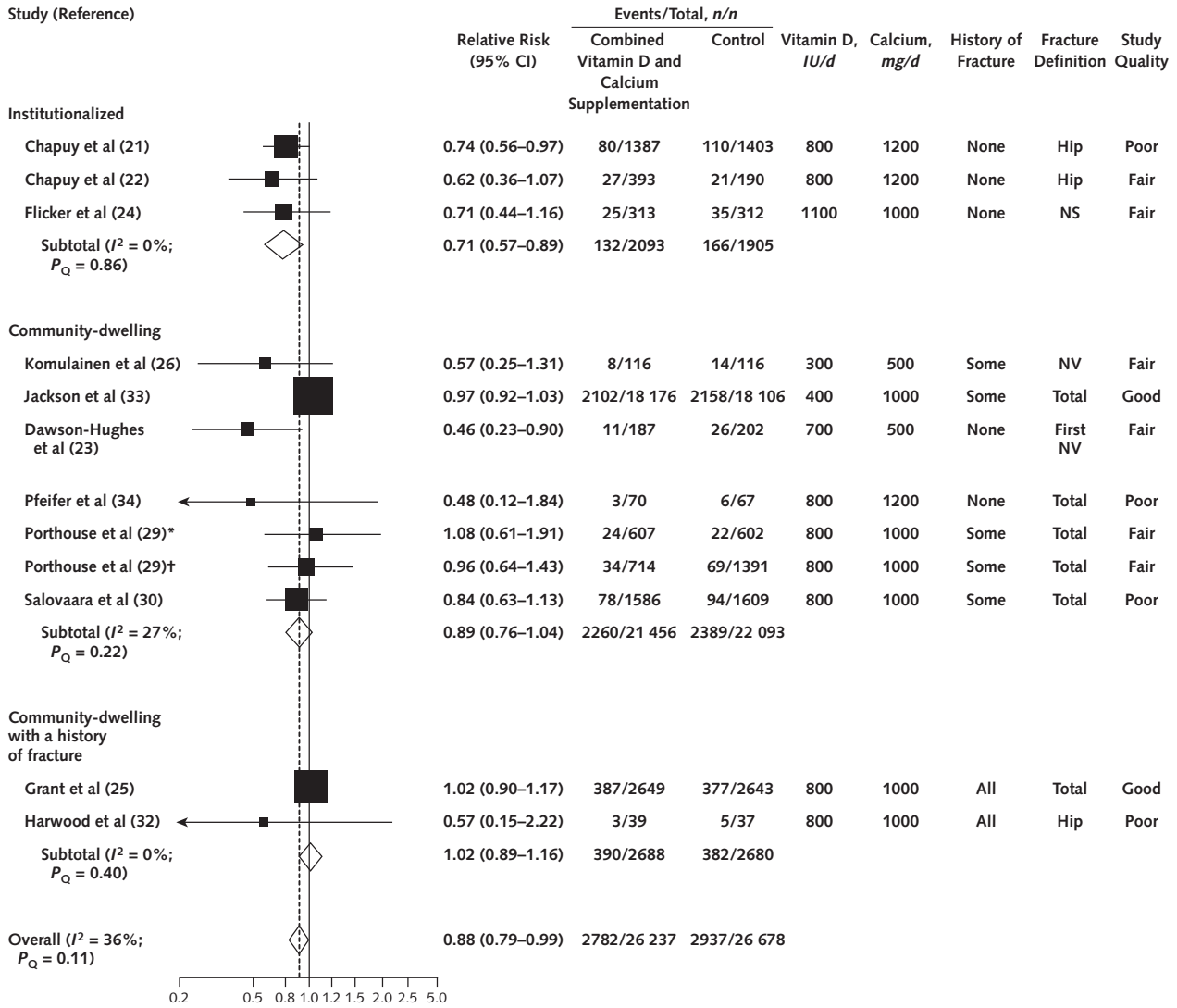
Meta-regression analyses did not show differential effects depending on the daily dose of vitamin D supplementation (16 studies included; risk ratio per 100-IU increase in dose, 1.01 [CI, 0.97 to 1.07]) or the baseline blood 25-(OH)D concentration (12 studies included; risk ratio per 100-IU increase in concentration, 1.02 [CI, 0.86 to 1.2]).

Associations Between Vitamin D Status and Cancer and Fracture Outcomes
Cancer

We included 28 observational studies: Three prospective cohort and 25 nested case–control studies evaluated the associations between baseline vitamin D status and risk for total cancer (35–37) or colorectal (19, 38–45), prostate (46–56), or breast (57–61) cancer (**Supplement 3**, available at www.annals.org). One (4%), 17 (61%), and 10 (36%) of the 28 studies were of good, fair, and poor quality, respectively (**Appendix Figure 5**, available at www

Figure 2. Results of random-effects model meta-analysis of the effects of combined vitamin D and calcium supplementation as compared with placebo on total fracture in randomized, controlled trials.

Study (Reference)	Relative Risk (95% CI)	Events/Total, *n/n* Combined Vitamin D and Calcium Supplementation	Control	Vitamin D, IU/d	Calcium, mg/d	History of Fracture	Fracture Definition	Study Quality
Institutionalized								
Chapuy et al (21)	0.74 (0.56–0.97)	80/1387	110/1403	800	1200	None	Hip	Poor
Chapuy et al (22)	0.62 (0.36–1.07)	27/393	21/190	800	1200	None	Hip	Fair
Flicker et al (24)	0.71 (0.44–1.16)	25/313	35/312	1100	1000	None	NS	Fair
Subtotal (*I*² = 0%; *P*_Q = 0.86)	0.71 (0.57–0.89)	132/2093	166/1905					
Community-dwelling								
Komulainen et al (26)	0.57 (0.25–1.31)	8/116	14/116	300	500	Some	NV	Fair
Jackson et al (33)	0.97 (0.92–1.03)	2102/18 176	2158/18 106	400	1000	Some	Total	Good
Dawson-Hughes et al (23)	0.46 (0.23–0.90)	11/187	26/202	700	500	None	First NV	Fair
Pfeifer et al (34)	0.48 (0.12–1.84)	3/70	6/67	800	1200	None	Total	Poor
Porthouse et al (29)*	1.08 (0.61–1.91)	24/607	22/602	800	1000	Some	Total	Fair
Porthouse et al (29)†	0.96 (0.64–1.43)	34/714	69/1391	800	1000	Some	Total	Fair
Salovaara et al (30)	0.84 (0.63–1.13)	78/1586	94/1609	800	1000	Some	Total	Poor
Subtotal (*I*² = 27%; *P*_Q = 0.22)	0.89 (0.76–1.04)	2260/21 456	2389/22 093					
Community-dwelling with a history of fracture								
Grant et al (25)	1.02 (0.90–1.17)	387/2649	377/2643	800	1000	All	Total	Good
Harwood et al (32)	0.57 (0.15–2.22)	3/39	5/37	800	1000	All	Hip	Poor
Subtotal (*I*² = 0%; *P*_Q = 0.40)	1.02 (0.89–1.16)	390/2688	382/2680					
Overall (*I*² = 36%; *P*_Q = 0.11)	0.88 (0.79–0.99)	2782/26 237	2937/26 678					

NS = not specified; NV = nonvertebral.
* Equally allocated groups.
† Unequally allocated groups; 2 women were randomly assigned to the control group for every 1 woman randomly assigned to the treatment group.

.annals.org). Common limitations among the fair- or poor-quality observational studies were lack of adjustment of family history of cancer in the analyses, lack of justification of final statistical models, and unclear reporting of blinding of exposure or outcome assessors (**Appendix Figure 6**, available at www.annals.org).

Three prospective cohorts (1 of good quality; 2 of fair quality) examined the associations between baseline vitamin D status and risk for total cancer mortality in 19 503 men and women (35–37), 86% of whom were from 1 study (36) in the United States (only this study included women). The mean follow-up ranged from 7 to 14 years, and the incidence of total cancer deaths ranged from 53 to

158 per 1000 persons. All studies observed higher baseline blood 25-(OH)D concentrations with increased risks for total cancer mortality among men, but this association was not found among women (reported in 1 study [36]). The ranges of blood 25-(OH)D concentrations and the shapes of the dose–response relationships varied across studies (**Supplement 4**, available at www.annals.org).

Of the 25 nested case–control studies included, 9 reported a colorectal cancer outcome (19, 38–45), 11 reported a prostate cancer outcome (46–56), and 5 reported a breast cancer outcome (57–61). The cancer outcomes were self-reported, with verification against medical records or linkage

data from cancer registries in most studies; all stages of cancer were included.

For colorectal cancer, most studies found an inverse relationship with prediagnosis blood 25-(OH)D concentration (**Figure 3**, *top*). Our dose–response meta-analysis of 9 nested case–control studies showed that each 10-nmol/L increase in prediagnosis blood 25-(OH)D concentration was associated with a 6% (CI, 3% to 9%) reduction in risk for colorectal cancer (**Table 2**).

For prostate cancer, 3 poor-quality studies (with a total of 1147 cases) provided insufficient data for our dose–response meta-analyses (48, 51, 56). Findings from individual studies were mixed, and some studies suggested a nonlinear relationship (**Figure 3**, *middle*). Our dose–response meta-analysis of 8 nested case–control studies showed that each 10-nmol/L increase in prediagnosis blood 25-(OH)D concentration was not associated with risk for prostate cancer (**Table 2**).

For the female breast cancer outcome, 1 poor-quality study (of 142 cases) provided insufficient data for our dose–response meta-analyses (61). Only this study (not shown in the figure) and 1 of the remaining 4 studies found that higher prediagnosis blood 25-(OH)D was associated with a lower risk for breast cancer (**Figure 3**, *bottom*). Our dose–response meta-analysis of the 4 nested case–control studies showed that each 10-nmol/L increase in prediagnosis blood 25-(OH)D concentration was not associated with risk for breast cancer (**Table 2**).

Fractures

A brief summary of the findings of the relationships between vitamin D status and fracture risk from the University of Ottawa Evidence-based Practice Center evidence report (8) is presented in **Table 1**.

Effects of Vitamin D With or Without Calcium on Changes in Vitamin D Status

In our 2009 evidence report (5), we used a scatterplot to evaluate the net changes in blood 25-(OH)D concentration (that is, between-group differences in the change from baseline) against the doses of vitamin D supplementation using data from 26 RCTs of adults (**Appendix Figure 7**, available at www.annals.org). The plot showed a clear relationship between increasing dose of vitamin D_3 and increasing net change in blood 25-(OH)D concentration.

Adverse Events Associated With Vitamin D With or Without Calcium

The Women's Health Initiative trial found an increase in the risk for renal and urinary tract stones with supplementation (hazard ratio, 1.17 [CI, 1.02 to 1.34] for both outcomes) (18, 19, 62). No other identified study evaluated the effects of vitamin D with or without calcium supplements on renal outcomes.

Most of the RCTs included in our 2009 evidence report (5) and from our update did not provide information on adverse events and were not adequately powered to detect adverse events. Other RCTs reported a few cases of gastrointestinal disruption (such as constipation, diarrhea, or upset stomach), musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi. However, these adverse events may or may not be associated with the vitamin D or calcium supplements.
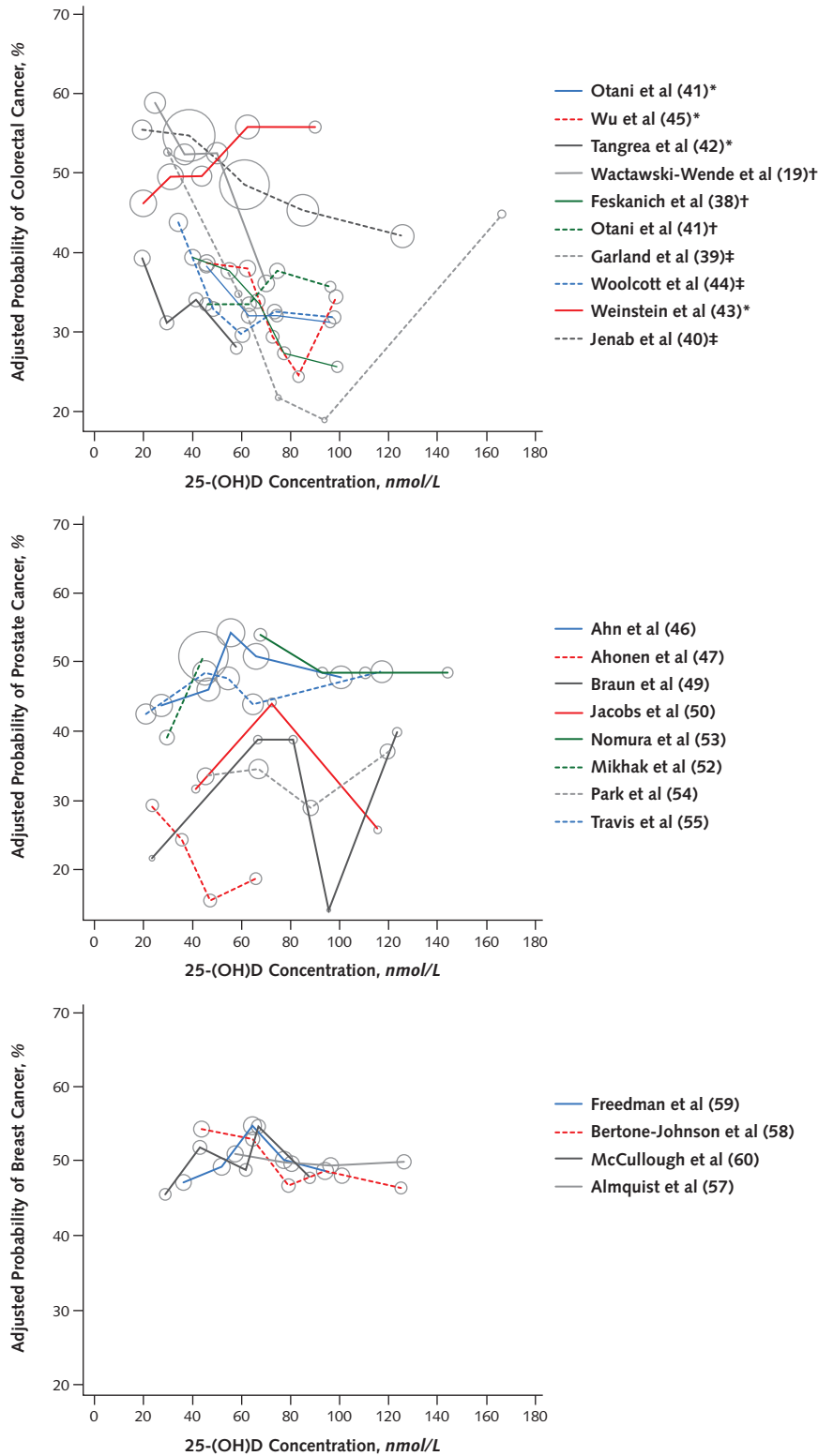
DISCUSSION

On the basis of the aggregate internal validity of the body of evidence for each key question—in turn based on the number, methodological quality, and size of studies; consistency of results between studies; and directness of evidence—we concluded that combined vitamin D (300 to 1100 IU/d) and calcium supplementation (500 to 1200 mg/d), but not vitamin D supplementation alone, can reduce the fracture risk in older adults. However, the effects may vary according to setting, with smaller effects in community-dwelling elderly persons or postmenopausal women than in institutionalized elderly persons. The evidence is not sufficiently robust to draw a conclusion about the benefits or harms of vitamin D supplementation for cancer prevention. Direct evidence from RCTs for the effects of vitamin D (with or without calcium) supplementation on cancer outcomes is limited and does not agree with data from observational studies. Limited data from RCTs suggest that a high dosage (1000 IU/d) of vitamin D can reduce the risk for total cancer.

Although data from observational studies suggest that higher blood 25-(OH)D concentrations may be associated with increased risks for total cancer, the threshold of a "safe" concentration remains unclear. Observational studies also suggest that the relationship between blood 25-(OH)D concentrations and risk for cancer may be site-specific and can vary across different populations. For example, our analyses showed that higher blood 25-(OH)D concentrations were associated with a reduced risk for colorectal cancer but not breast or prostate cancer. These results, however, are limited by the methodological quality of the included observational studies, particularly regarding the potential for residual confounding. Other issues that must be considered in interpreting the results from observational studies include shifts in methodological approaches to measure serum 25-(OH)D concentrations, the latitude or study location, and the time of year when blood was sampled.

Because of these issues, as well as the limitations of study-level meta-analysis (such as ecologic and publication bias) (63), the results of our dose–response meta-analyses must be interpreted with caution. One cannot predict the effects on the pooled effect estimates if these biases exist.

The Women's Health Initiative trial is the largest RCT included in the current review. This trial was rated as a good-quality effectiveness trial (in contrast with a more standardized efficacy trial) on the basis of supporting deci-

Figure 3. **Relationships between prediagnosis blood 25-(OH)D concentrations and risks for colorectal, prostate, and breast cancer in individual nested case–control studies included in the dose–response meta-analyses.**

Colorectal cancer panel legend:
— Otani et al (41)*
- - - Wu et al (45)*
— Tangrea et al (42)*
— Wactawski-Wende et al (19)†
— Feskanich et al (38)†
- - - Otani et al (41)†
- - - Garland et al (39)‡
- - - Woolcott et al (44)‡
— Weinstein et al (43)*
- - - Jenab et al (40)‡

Prostate cancer panel legend:
— Ahn et al (46)
- - - Ahonen et al (47)
— Braun et al (49)
— Jacobs et al (50)
— Nomura et al (53)
- - - Mikhak et al (52)
- - - Park et al (54)
- - - Travis et al (55)

Breast cancer panel legend:
— Freedman et al (59)
- - - Bertone-Johnson et al (58)
— McCullough et al (60)
— Almquist et al (57)

Circle size is proportional to the number of cancer cases relative to all other studies included in the same panel. See the **Appendix** (available at www.annals.org) for methods used for the dose–response meta-analyses. 25-(OH)D = 25-hydroxyvitamin D.
* Men. † Women. ‡ Both men and women.

Table 2. Results of Linear Mixed-Effects Meta-Regression to Examine the Dose–Response Relationships Between Each 10-nmol/L Increase in Prediagnosis Blood 25-Hydroxyvitamin D Concentration and the Risks for Colorectal, Prostate, and Breast Cancer in Nested Case–Control Studies

Outcome	Studies (References)	Methodologic Quality	Case-Patients and Controls, n*	Pooled Adjusted OR (95% CI)†	P Value
Colorectal cancer	9 nested case–control studies (19, 38–45)	8 fair, 1 poor	1127 case-patients 1122 controls	0.94 (0.91–0.97)	<0.001
Prostate cancer	8 nested case–control studies (46, 47, 49, 50, 52–55)	4 fair, 4 poor	2399 case-patients 3210 controls	1.01 (0.99–1.04)	0.35
Female breast cancer	4 nested case–control studies (57–60)	3 fair, 1 poor	2363 case-patients 2363 controls	0.99 (0.97–1.01)	0.42

OR = odds ratio.
* Effective counts of case-patients and controls. See the Appendix (available at www.annals.org) for methods used for the dose–response meta-analyses.
† Different covariates were adjusted across studies.

sion making about whether to actively recommend supplementation for an individual woman in the real-world setting. Critics of this study have pointed to the "low dosage" (400 IU/d) of vitamin D supplementation, lack of blood 25-(OH)D measurement, poor adherence, low baseline risk of the study population, and off-study use of additional vitamin D and calcium supplements during the trial as factors that could explain the null findings (64–66). Others have suspected that the adverse outcomes of renal and urinary stones were associated with excess calcium intake from both diet and calcium supplements (67). These concerns raise many important issues regarding the design and conduct of future trials of dietary supplements, which need to consider the myriad differences between nutrients and drugs, especially when the background exposure to a nutrient (such as vitamin D) cannot be reliably ascertained.

Current understanding of the benefits and harms of vitamin D (with or without calcium) supplements in the general population is chiefly limited by the difficulties in evaluating true vitamin D status. No methods are currently available to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure on an individual or a group, and serious limitations remain in accurately estimating dietary vitamin D intake because of the incompleteness of nutrient databases for both vitamin D–fortified food and vitamin D supplements. Moreover, the addition of vitamin D supplements to vitamin D taken in through all other means may exceed the safe level, resulting in harmful events (68, 69). This caution is supported by the recent finding from a randomized, double-blind, placebo-controlled trial examining the effects of a single annual megadose of vitamin D_3 (500 000 IU, equivalent to approximately 1370 IU/d) on fall and fracture outcomes in community-dwelling elderly women with a history of fall or fracture (31). This RCT used the highest daily dose of vitamin D_3 of all included RCTs and demonstrated that the megadose increased the risk for fractures and falls. Future study is needed to evaluate the appropriate dose and dosing regimens of vitamin D supplementation for bone health outcomes.

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APPENDIX

A total of 33 publications met our eligibility criteria for KQ 2 (the associations between vitamin D status and the clinical outcomes of cancer), but 5 publications were excluded because they were superseded by later publications in the same cohort with more cancer cases (70–73). Many cohorts had multiple publications reporting different cancer outcomes of interest. There was no overlap in study populations in each cancer out-

come in our systematic review and in each dose–response meta-regression.

We performed linear dose–response meta-regressions to examine the associations between blood 25-(OH)D concentrations and the risk for prostate and colorectal cancers by using a mixed-effect logistic regression model. Specifically, we fitted a mixed-effects meta-regression (with fixed intercepts and random slopes) using the exact binomial likelihood, which explicitly models between-study variability in the strength of the dose–response relationship. For each study, we back-calculated the "effective counts" of events in each category of 25-(OH)D concentration based on the pertinent adjusted log odds ratios (vs. a reference exposure category), their variance, and the total number of participants per exposure category and by solving a set of nonlinear equations (74). The effective counts of events are such that when used in a logistic regression with the exposure categories as the sole predictors, they result in the same log odds ratios (coefficients), variances, and covariances as those from the original adjusted model. The mean value per exposure category of 25-(OH)D concentration is also needed for dose–response meta-regressions. When it was not reported, the midpoint between exposure category thresholds was selected, and for the open categories, we imputed a mean intake 20% lower for the lowest quintile threshold or 20% higher for the highest quintile threshold, respectively.

To show the individual study results in **Figure 3**, we calculate the adjusted probability of cancer (odds/[1 + odds]) by using the effective numbers of case-patients and controls and plotted against the mean value of each exposure category of 25-(OH)D concentration.

Appendix Figure 1. **Analytic framework and study questions.**
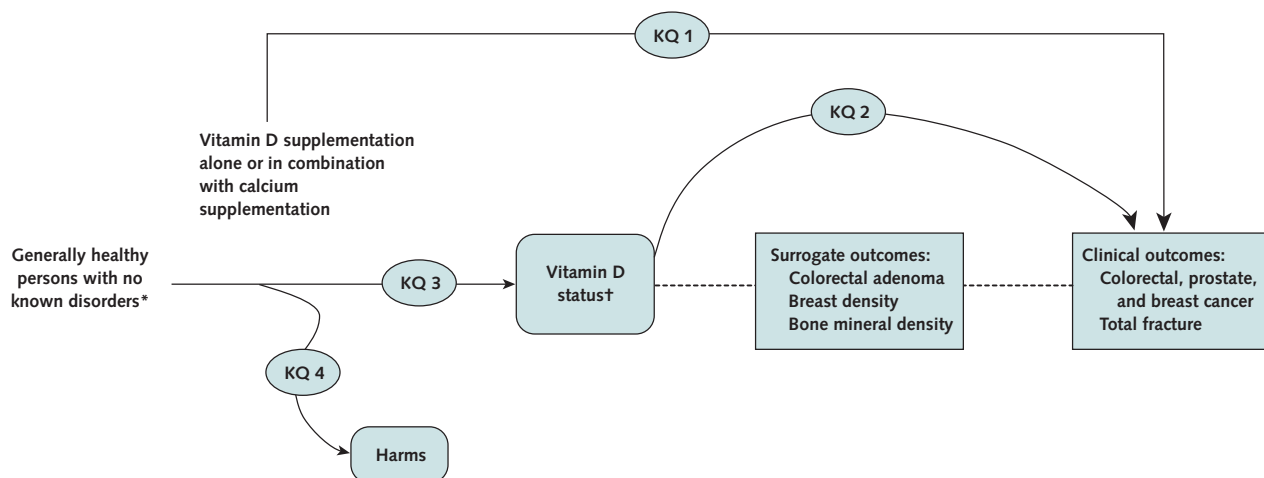

KQs

1. What are the effects of vitamin D alone or in combination with calcium supplements on the clinical outcomes of cancer and fractures?
2. What are the associations between vitamin D status and clinical outcomes of cancer and fractures?
3. What are the effects of vitamin D alone or in combination with calcium supplements on the net changes in vitamin D status?
4. What are the adverse outcomes associated with vitamin D and calcium supplements?

KQ = key question.
* See "Study Selection" section for detailed population of interest.
† Blood 25-hydroxyvitamin D concentration was used as the indicator of vitamin D status.

*Appendix Figure 2.* **Summary of evidence search and selection.**
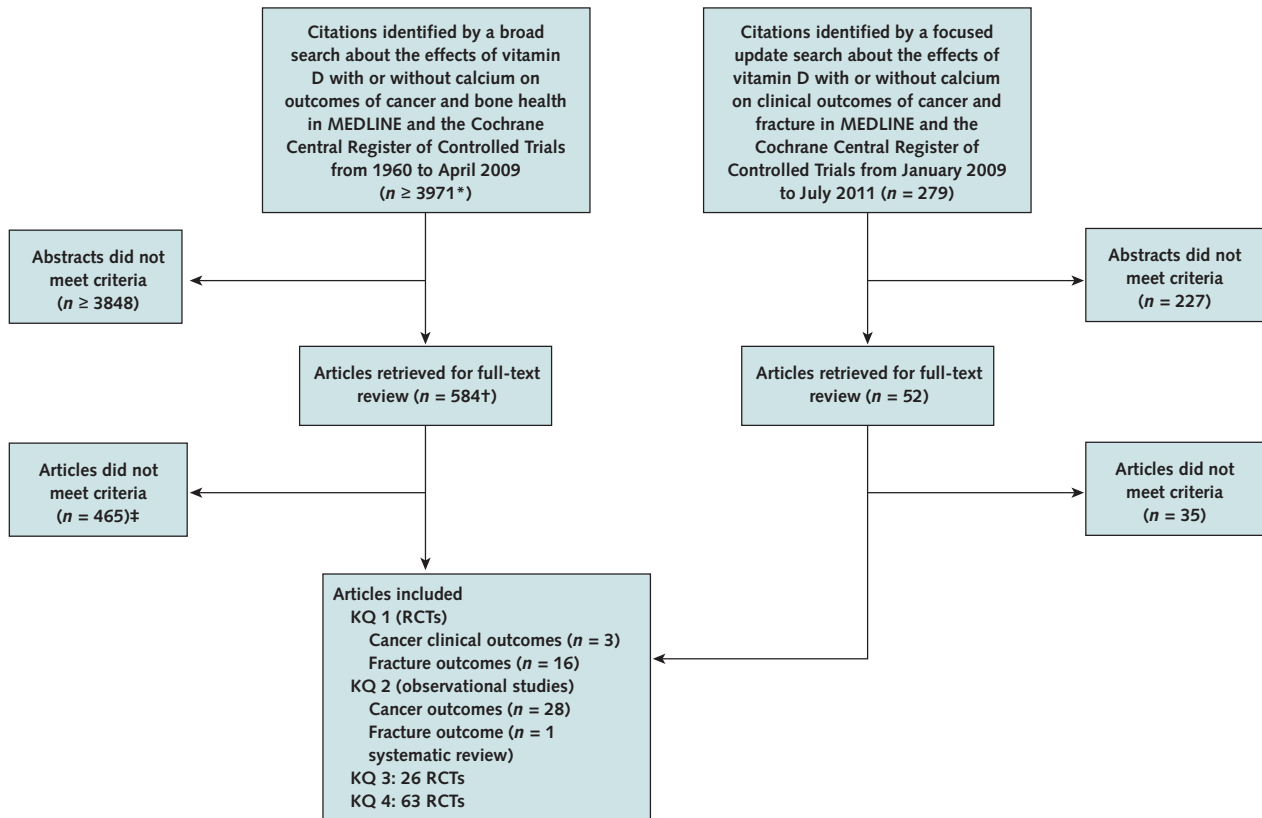
KQ = key question; RCT = randomized, controlled trial.
* A total of 16 733 citations were screened for a wide array of clinical outcomes. The 3971 citations refer to those specifically from the cancer and bone health search, but potentially relevant citations from searches for other outcomes were also screened for cancer and bone health outcomes.
† A total of 584 full-text articles were retrieved for review for a wide array of clinical outcomes, including cancer and bone health outcomes.
‡ Reasons for exclusion are in the 2009 evidence report (5).

Appendix Figure 3. Quality assessment of 3 RCTs examining the effects of vitamin D with or without calcium supplementation on cancer outcomes.
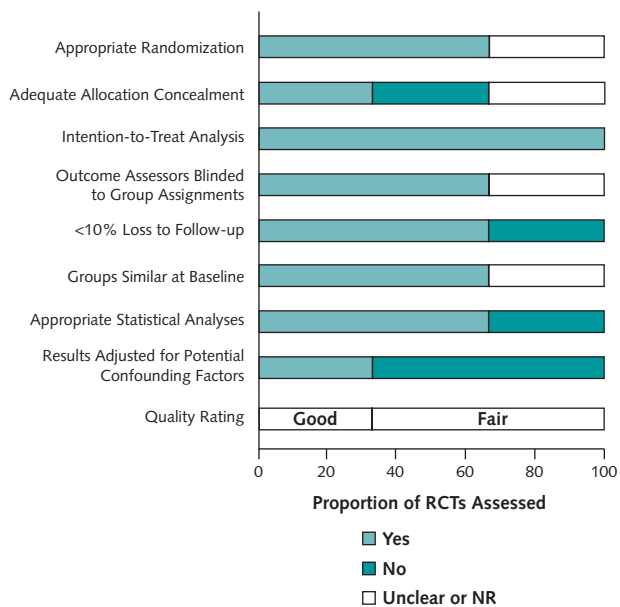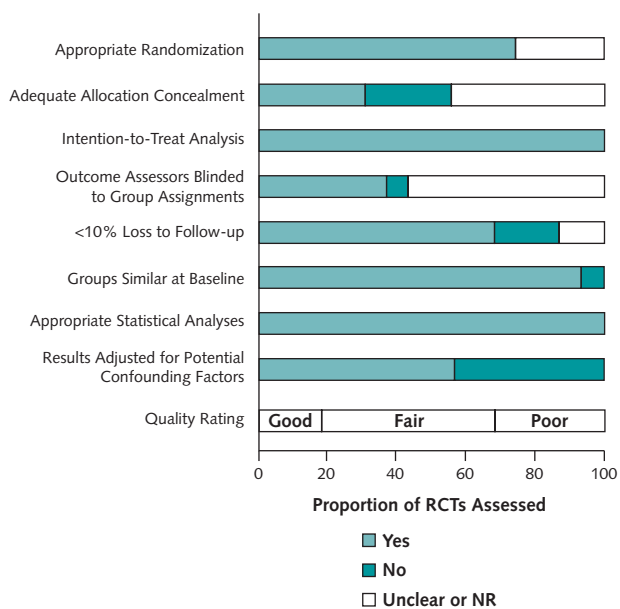

NR = not reported; RCT = randomized, controlled trial.

Appendix Figure 5. Distribution of quality rating in 3 prospective cohort and 25 nested case–control studies evaluating the associations between baseline vitamin D status and risks for any cancer, as well as colorectal, prostate, or breast cancer.
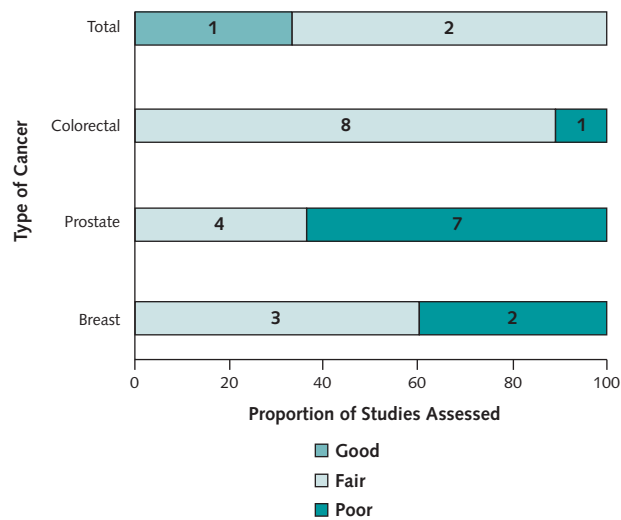

Numbers on the bars indicate the number of studies.

Appendix Figure 4. Quality assessment of 16 RCTs examining the effects of vitamin D with or without calcium supplementation on fracture outcomes.


NR = not reported; RCT = randomized, controlled trial.

Appendix Figure 6. Quality assessment of observational studies examining the associations between baseline vitamin D status and risk for cancer.
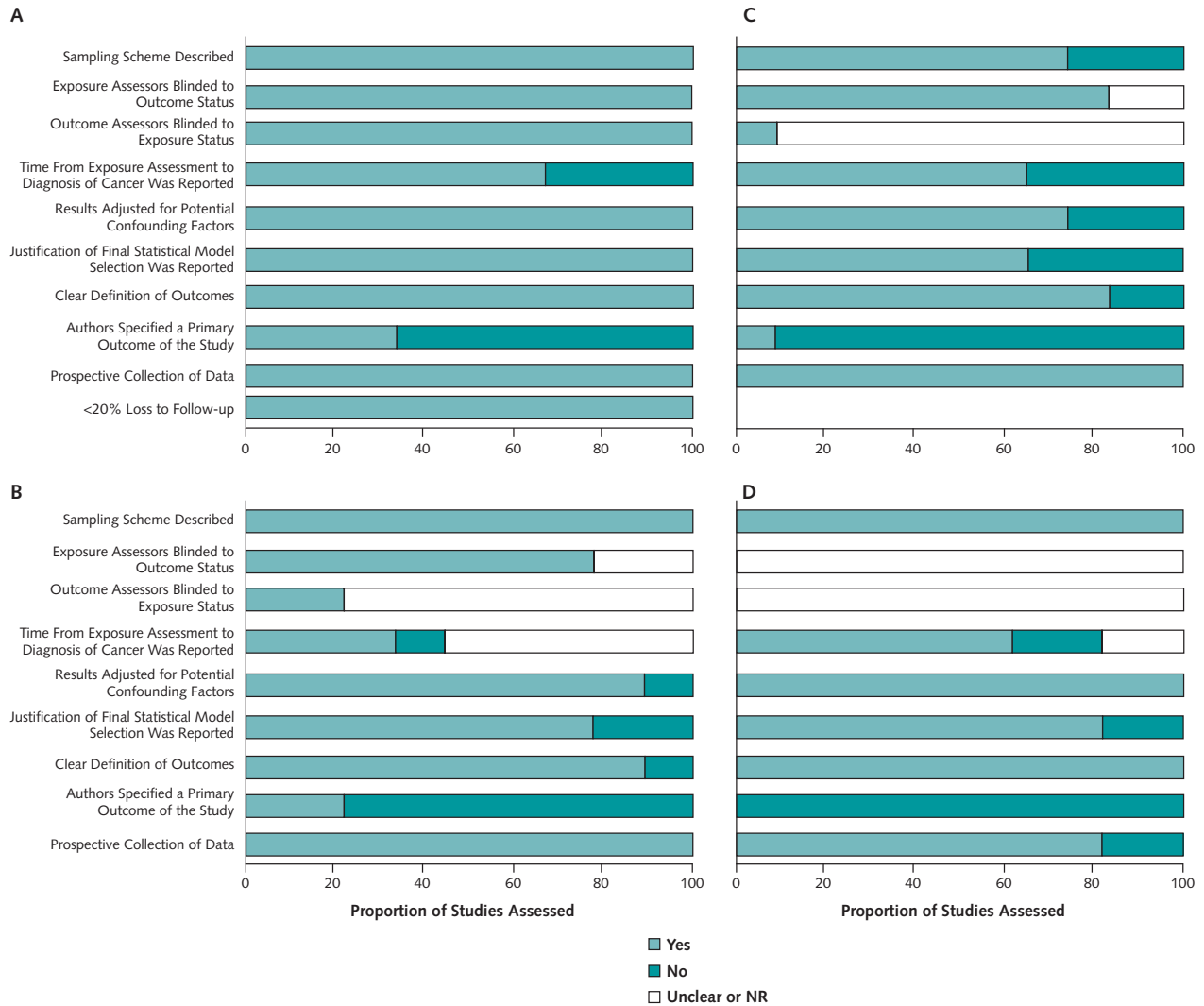
Quality item "<20% loss to follow-up" was applicable only to prospective cohort studies (total cancer outcome). **A.** Three prospective cohort studies reporting total cancer outcome. **B.** Nine nested case–control studies reporting colorectal cancer outcome. **C.** Eleven nested case–control studies reporting prostate cancer outcome. **D.** Five nested case–control studies reporting breast cancer outcome.

Appendix Figure 7. Effects of vitamin D with or without calcium supplementation on the net changes in serum 25-(OH)D concentrations.
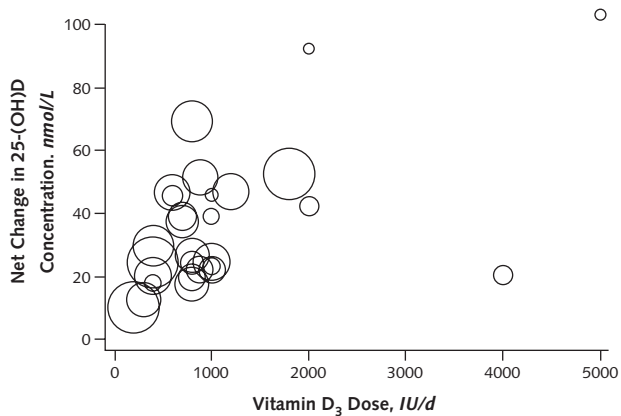
We explored the dose–response relationships between the doses of vitamin D (with or without calcium) and net changes in serum 25-(OH)D concentrations graphically, using a scatterplot where the observed net changes in 25-(OH)D concentration were plotted against the doses of vitamin D_3 supplementation. Studies were included only if they reported sufficient data to estimate both mean net change and SE of the net change. Calculations of mean net change and SE of the net change were described elsewhere (5). Each circle represents an RCT. The size of the circle is proportional to the sample size of the RCT. A total of 26 RCTs were included (21, 23, 34, 75–97). 25-(OH)D = 25-hydroxyvitamin D; RCT = randomized, controlled trial.