

Systematic Review with Meta-Analysis

Calcium supplements and cancer risk: a meta-analysis of randomised controlled trials

Sarah M. Bristow¹, Mark J. Bolland^{1*}, Graeme S. MacLennan², Alison Avenell², Andrew Grey¹, Greg D. Gamble¹ and Ian R. Reid¹

¹Bone Research Group, Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand

²Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

(Submitted 6 September 2012 – Final revision received 6 March 2013 – Accepted 7 March 2013 – First published online 19 April 2013)

Abstract

Some evidence suggests that Ca and vitamin D supplements affect cancer risk; however, it is uncertain whether the effects are due to Ca, vitamin D or the combination. We investigated the effect of Ca supplements without co-administered vitamin D on cancer risk. Medline, Embase and the Cochrane Central Register of Controlled Trials, reference lists of meta-analyses and two clinical trial registries were searched for randomised, placebo-controlled trials of Ca supplements (≥ 500 mg/d), with ≥ 100 participants and duration > 1 year. The lead authors of eligible trials supplied data on cancer outcomes. Trial-level data were analysed using random-effects meta-analyses and patient-level data using Cox proportional hazards models. A total of sixteen trials were eligible, six had no data available, ten provided trial-level data (n 10 496, mean duration 3.9 years), and of these, four provided patient-level data (n 7221, median duration 3.5 years). In the meta-analysis of trial-level data, allocation to Ca did not alter the risk of total cancer (relative risk 0.95, 95% CI 0.76, 1.18, $P=0.63$), colorectal cancer (relative risk 1.38, 95% CI 0.89, 2.15, $P=0.15$), breast cancer (relative risk 1.01, 95% CI 0.64, 1.59, $P=0.97$) or cancer-related mortality (relative risk 0.96, 95% CI 0.74, 1.24, $P=0.75$), but reduced the risk of prostate cancer (relative risk 0.54, 95% CI 0.30, 0.96, $P=0.03$), although there were few events. The meta-analysis of patient-level data showed similar results, with no effect of Ca on the risk of total cancer (hazard ratio 1.07, 95% CI 0.89, 1.28, $P=0.50$). Ca supplements without co-administered vitamin D did not alter total cancer risk over 4 years, although the meta-analysis lacked power to detect very small effects, or those with a longer latency.

Key words: Calcium supplements: Cancer: Meta-analysis: Randomised trials

It is possible that Ca intake has an impact on cancer risk, with some observational studies suggesting that high intakes of Ca and/or vitamin D are associated with a reduced risk of colorectal^(1–3) and breast cancer^(4,5), and an increased risk of prostate cancer^(6–8); however, these results are not consistent^(9–14). To date, few randomised, placebo-controlled trials of Ca supplements with or without vitamin D have reported cancer outcomes. In a 4-year fracture prevention trial, Lappe *et al.*⁽¹⁵⁾ reported that Ca monotherapy decreased total cancer risk by 47% ($P=0.06$), and Ca with vitamin D by 60% ($P=0.01$).

In contrast, three randomised, placebo-controlled trials^(16–19) of Ca with or without vitamin D have found no evidence of an effect on cancer risk. We found no effect of Ca monotherapy on total cancer incidence in a 5-year trial in postmenopausal

women⁽¹⁹⁾. The Randomised Evaluation of Calcium Or Vitamin D (RECORD) investigators found no effect of Ca with or without vitamin D on cancer mortality or incidence in older people treated for a median of 45 months⁽¹⁶⁾. The Women's Health Initiative (WHI) investigators reported no effect of Ca plus vitamin D on the risk of colorectal⁽¹⁸⁾ or breast⁽¹⁷⁾ cancer in > 36 000 postmenopausal women treated for an average of 7 years. However, we recently reanalysed the publicly available WHI dataset and found significant interactions between treatment allocation, personal Ca or vitamin D supplement use and the risk of total, breast and colorectal cancers, suggesting that widespread personal (non-protocol) supplement use may have obscured a therapeutic effect of Ca and vitamin D on cancer endpoints⁽²⁰⁾. When analyses

Abbreviations: RECORD, Randomised Evaluation of Calcium Or Vitamin D; WHI, Women's Health Initiative.

* **Corresponding author:** M. J. Bolland, fax +64 9 373 7677, email m.bolland@auckland.ac.nz

were restricted to participants not taking personal Ca or vitamin D at baseline, Ca and vitamin D significantly reduced the risk of total and breast cancer by 14–20%, and non-significantly reduced the risk of colorectal cancer by 17%.

Thus, there is some evidence that Ca and vitamin D supplements might lower cancer risk; however, it remains uncertain whether these possible effects are related to Ca, vitamin D or the combination of both agents. We have updated a large database of randomised clinical trials of Ca supplements in older adults, originally assembled to assess the effect of Ca supplements on cardiovascular risk, to determine whether Ca used as a monotherapy has an impact on cancer risk.

Methods

In November 2007, Medline, Embase and Cochrane Central were searched for randomised, placebo-controlled trials of Ca supplements, using the terms ‘calcium’, ‘randomised controlled trial’ and ‘placebo’ as text words, and corresponding Medical Subject Headings (MeSH) terms. The reference lists of meta-analyses published between 1990 and 2007 on the effect of Ca supplements on fracture, bone density, colorectal neoplasia and blood pressure, and two clinical trial registries (ClinicalTrials.gov and Australian New Zealand Clinical Trial Registry) were searched. No language restrictions were applied⁽²¹⁾. In February 2012, searches of the electronic databases were updated (Medline: 1966–February 2012; Embase: 1980–February 2012; Cochrane Central: January 2012).

Study selection

Studies were included if they were randomised, double-blind, placebo-controlled trials; the mean age of participants at baseline was >40 years; a dose of ≥500 mg/d of elemental Ca was administered; ≥100 participants were randomised; participants of either sex were studied; and the duration of the trial was >1 year. Studies were excluded if Ca and vitamin D were co-administered and compared with placebo (studies were eligible if vitamin D was given to both intervention and control groups); if Ca was administered in the form of a complex nutritional supplement or as a dietary modification; and if most participants had a major systemic disease other than osteoporosis or colorectal adenoma.

Search results

For the present review, two investigators carried out the search (M. J. B. and S. M. B.) and two investigators independently reviewed all potential studies (M. J. B. and A. G.) to determine the adequacy of randomisation, the concealment of allocation, the blinding of participants and investigators and the extent of loss to follow-up.

Data description

The lead author of each eligible trial was invited to provide patient-level data for cancer outcomes for their study. When such data were not available, we requested trial-level

summary data. Complete trial-level data were available on total cancer events for seven studies (9447 participants)^(15,22–27), on colorectal cancer for eight studies (9863 participants)^(15,22–28), on breast cancer for six studies (7641 participants)^(15,22–26), on prostate cancer for three studies (1806 participants)^(23,25,27) and on cancer-related mortality for six studies (8109 participants)^(22,23,25–28). Partially complete trial-level data were available on total cancer for a further three studies (1049 participants)^(28–30), and on colorectal and breast cancer for a further two studies (633 participants)^(29,30). Of the studies that supplied complete trial-level data, patient-level data were also available on total cancer and colorectal cancer events for four studies (7221 participants)^(22,25–27), on breast cancer events for three studies (6087 participants)^(22,25,26) and on prostate cancer events for two studies (1134 participants)^(25,27). No data on cancer events were available for six studies (2743 participants)^(31–36).

We therefore had complete trial-level data on total cancer events for 71% of participants, at least partially complete trial-level data for 79% of participants, patient-level data for 54% of participants and no data for 21% of participants, from sixteen eligible trials.

Ascertainment of cancer events

For seven studies, data on cancer events were supplied by the lead authors. Data were obtained from a combination of self-reports, hospital discharge data and death certificates^(22,24–27,29,30) and cancer registries⁽²⁵⁾. For one study, data on prostate cancer⁽³⁷⁾ and colorectal cancer⁽²³⁾ were obtained

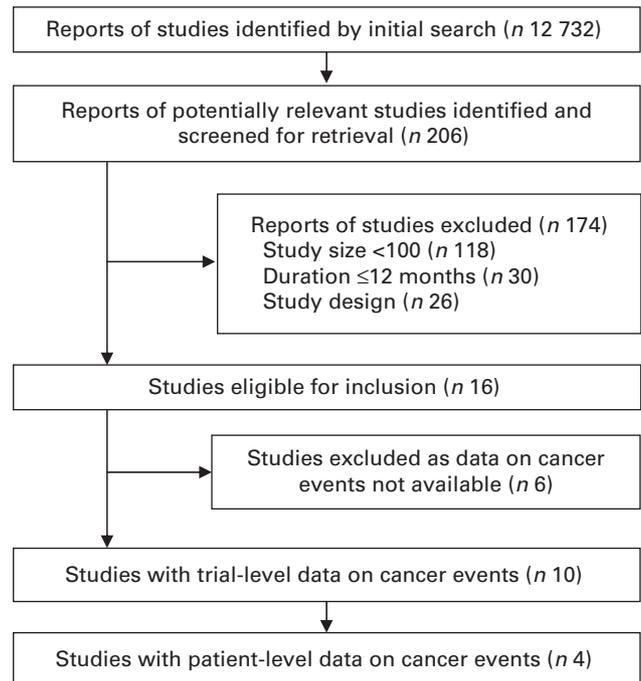


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of studies. The initial search was in November 2007 with 9358 reports identified, 173 reports of potentially relevant studies retrieved, 150 reports excluded and twenty-three reports of fifteen individual studies identified. The search was updated in March 2010 and February 2012: a further 3374 reports were identified, thirty-three reports retrieved and one new study identified.

Table 1. Characteristics of the sixteen studies eligible for inclusion in the meta-analysis

Studies	Ca-only group (n)	Control group (n)	Daily dose and supplement type	Trial duration (years)	Primary endpoint in the original trial	Baseline mean age (years)	Female (%)
Patient-level data on cancer outcomes							
Reid <i>et al.</i> ⁽²²⁾	68	67	1 g lactogluconate–carbonate	4	Bone mineral density	58	100
Grant <i>et al.</i> ^(16,25)	2617	2675	1 g carbonate	4*	Low trauma fracture	77	85
Reid <i>et al.</i> ^(19,26)	732	739	1 g citrate	5	Clinical fracture	74	100
Reid <i>et al.</i> ⁽²⁷⁾	216	107	0.6 or 1.2 g citrate	2	Spine bone mineral density	56	0
Subtotal/average†	3633	3588	–	4.1	–	75.5	87.1
Trial-level data on cancer outcomes‡							
Riggs <i>et al.</i> ⁽³⁰⁾	119	117	1.6 g citrate	4	Bone mineral density	66	100
Baron <i>et al.</i> ^(23,37)	464	466	1.2 g carbonate	4	Recurrence of colorectal adenoma	61	28
Bonithon-Kopp <i>et al.</i> ⁽²⁸⁾	204	212	2 g lactogluconate–carbonate	3	Recurrence of colorectal adenoma	59	37
Lappe <i>et al.</i> ⁽¹⁵⁾	445	288	1.4 g citrate or 1.5 g carbonate	4	Fracture incidence	67	100
Bonnick <i>et al.</i> ⁽²⁴⁾	282	281	1.25 g carbonate	2	Spine bone mineral density	66	100
Chailurkit <i>et al.</i> ⁽²⁹⁾	201	196	0.5 g carbonate	2	PTH and bone mass	66	100
Subtotal/average†	1715	1560	–	3.3	–	63.7	67.8
Total/average†	5348	5148	–	3.9	–	72.3	82.0
No data on cancer outcomes							
Smith <i>et al.</i> ⁽³²⁾	84	85	1.5 g carbonate	4	Arm bone mineral density	51	100
Dawson-Hughes <i>et al.</i> ⁽³⁶⁾	238	123	0.5 g carbonate or citrate	2	Spine bone mineral density	58	100
Elders <i>et al.</i> ⁽³³⁾	198	97	1 or 1.2 g lactogluconate –carbonate or citrate	2	Spine bone mineral density	NA	100
Recker <i>et al.</i> ⁽³⁴⁾	95	102	1.2 g carbonate	4	Vertebral fracture	74	100
Peacock <i>et al.</i> ⁽³¹⁾	126	135	0.75 g citrate	4	Hip bone mineral density	76	72
Prince <i>et al.</i> ⁽³⁵⁾	730	730	1.2 g carbonate	5	Osteoporotic fracture	75	100
Subtotal/average†	1471	1272	–	4.1	–	68.5	97.4

PTH, parathyroid hormone; NA, not available.

* Mean duration was 45 months, with all participants followed for at least 2 years during the trial.

† Weighted by person-years of follow-up.

‡ Complete trial-level data on total cancer events were available for seven studies^(15,22–27) and partially complete trial-level data were available for three studies^(28–30).

from published data, and data on total cancer, breast cancer and cancer mortality were supplied by the lead author and derived from hospital discharge data and death certificates. For another study, data on colorectal cancer were obtained from published data⁽²⁸⁾, and data on cancer-related mortality were supplied by the lead author and derived from physician-reported cause of death. For the final study, data on total, breast and colorectal cancers were obtained from published data⁽¹⁵⁾. The lead authors provided a description of each type of cancer events, and cancers described as 'skin', 'epidermal/epidermoid' or 'basal cell' or the International Classification of Diseases (ICD) code C44 were not considered in these analyses. For the one study for which total cancer events were obtained from published data⁽¹⁵⁾, the authors reported only total non-skin cancers. When data on cancer events were obtained from published data, data were extracted independently by two investigators (M. J. B. and S. M. B.).

Endpoints

The pre-specified primary endpoint was the incidence of first total cancer, excluding non-melanoma skin cancers. Secondary endpoints were the incidence of colorectal cancer, breast cancer, prostate cancer and cancer-related mortality.

Statistical analysis

The primary analysis was of trial-level data. Statistical heterogeneity was assessed using Cochran's *Q* statistic ($P < 0.10$) and the I^2 statistic ($I^2 > 50\%$). No significant statistical heterogeneity existed between trials in any of the analyses. Trial-level summary data were pooled using DerSimonian and Laird random-effects meta-analyses. Publication bias was assessed using funnel plots. Analyses were carried out using SAS version 9.2 or Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). All tests were two-tailed and $P < 0.05$ was considered as significant.

Studies that also provided patient-level data were included in a secondary patient-level analysis. Each endpoint was

analysed using a Cox proportional hazards model stratified by study, and the hazard ratio (HR) and 95% CI reported. The assumption of proportional hazards was explored graphically and by carrying out a test for proportionality of the interaction between variables included in the model and the logarithm of time. Assessment of the effect-modifying influence of covariates on outcomes was done by repeating the models including the following covariates potentially associated with cancer incidence: age, sex, smoking status, BMI and weight. This was also done by undertaking subgroup analyses using interaction terms between treatment allocation and the following pre-specified subgroups: sex, age (≥ 75 or < 75 years), dietary Ca (above or below the median for all studies), serum 25-hydroxyvitamin D (≥ 50 or < 50 nmol/l) and supplement type (citrate, carbonate or lactogluconate-carbonate), where data were available for $> 80\%$ of participants.

Based on the assumption that cancers diagnosed early on in the trials may have been present, but undetected, at baseline, we repeated these models including latent periods of 1 and 2 years. As a sensitivity analysis, the models were repeated including only the trials in which data were obtained from unverified sources (self-reports) or verified sources (cancer registries).

Results

The results of the literature search are shown in Fig. 1, and the characteristics of the eligible studies in Table 1. All ten eligible studies providing data were randomised, double-blind, placebo-controlled trials. The method of randomisation was stated in six trials: one used a centralised randomisation service and five used computer-generated random numbers. Allocation concealment was explicitly stated by four trials. Details of participants who were lost to follow-up or withdrew were reported by nine trials. All ten trials reported compliance; however, the definitions of compliance differed and were not always comparable. Table 2 shows the selected baseline characteristics of participants.

Table 2. Baseline variables in the trials with patient- or trial-level data available for cancer outcomes (Mean values and standard deviations)

Studies	Dietary Ca (mg/d)		25-Hydroxyvitamin D (nmol/l)		Weight (kg)		BMI (kg/m ²)		Current smoker (%)	History of colorectal adenoma (%)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Reid <i>et al.</i> ⁽²²⁾	750	290	93	37	65	9	25	3	10	NA
Riggs <i>et al.</i> ⁽³⁰⁾	710	290	80	25	NA		NA		NA	NA
Baron <i>et al.</i> ⁽³⁷⁾	880	440	73	27	82	15	27	4	19	100
Bonithon-Kopp <i>et al.</i> ⁽²⁸⁾	980	380		NA		NA		NA	NA	100
Grant <i>et al.</i> ^{(25)*}	820	350	38	16	65	12		NA	12	NA
Reid <i>et al.</i> ⁽²⁶⁾	860	390	54	18	67	11	26	4	3	NA
Reid <i>et al.</i> ⁽²⁷⁾	870	450	92	33	83	12	26	3	3	NA
Lappe <i>et al.</i> ⁽¹⁵⁾		1070†	72	20	77	15	29	6	NA	NA
Bonnick <i>et al.</i> ⁽²⁴⁾	1240	580		NA		NA		NA	0.4	NA
Chailurkit <i>et al.</i> ⁽²⁹⁾	375	210	69	19	59	8	25	3	NA	NA

NA, not available.

* 25-Hydroxyvitamin D measured in a sample of sixty participants.

† Value is median.

Trial-level analysis

There were seven studies that provided complete trial-level data on total cancer events and were included in the primary analysis. The number of people with cancer events in each study by treatment allocation is shown in Table 3, and the results of the trial-level analysis are shown in Fig. 2. Allocation to Ca supplements had no effect on the risk of total cancer, colorectal cancer, breast cancer or cancer-related mortality. Allocation to Ca supplements was associated with a significant decrease in the risk of prostate cancer. A further three trials^(28–30) for total cancer and two trials^(29,30) for colorectal and breast cancer had data only for subgroups of participants, and were included in a sensitivity analysis that included data from all ten trials. Including data from these further trials did not change the results for any endpoint. Publication bias was not evident on inspection of funnel plots in any analysis.

Patient-level analysis

Among the eligible trials, four studies that provided trial-level data also provided patient-level data and were included in a secondary patient-level analysis. The selected baseline characteristics are shown in Table 4, and the results in Table 5 and Fig. 3. The median duration of follow-up in both groups was 3.5 (interquartile range 2.6–4.4) years. Allocation to Ca supplements had no effect on the risk of total cancer, breast cancer or cancer-related mortality. Allocation to Ca supplements significantly increased the risk of colorectal cancer, and non-significantly decreased the risk of prostate cancer. Adjusting for pre-specified covariates likely to be related to cancer outcomes, with data available for more than 80% of participants (age, sex, smoking status and weight), did not change these results, nor did including trials in which data were obtained only from verified sources. Repeating the models including a latent period of 1 or 2 years to attempt to adjust for cancers that were present, but undetected at baseline, moved the results for colorectal cancer and prostate cancer towards significance, but did not alter the results in any other way (Table 5). In pre-specified subgroup analyses, no interactions were identified between treatment allocation and age, sex, vitamin D status, smoking status, dietary Ca intake and supplement type for any cancer endpoint.

Discussion

In the present meta-analysis of 10 500 participants from ten trials, Ca supplements without co-administered vitamin D did not alter the risk of total cancer, breast cancer or cancer-related mortality over 4 years. Ca supplements significantly reduced prostate cancer risk; however, this was based on a small number of events. Ca supplements did not alter colorectal cancer risk in the trial-level analysis, while there was an increased risk in the patient-level analysis; however, this was based on a small number of events. Including a latent period of 1 or 2 years did not meaningfully alter the results.

While the association between Ca intake and cancer risk has been the subject of numerous observational studies, few

Table 3. Number of people with cancer and cancer-related mortality by treatment group

Studies	Ca group					Control group						
	Randomised (n)	Total cancer*	Colorectal cancer	Breast cancer	Prostate cancer	Cancer mortality	Randomised (n)	Total cancer*	Colorectal cancer	Breast cancer	Prostate cancer	Cancer mortality
Reid <i>et al.</i> ⁽⁶²⁾	68	4	1	0	NP	0	67	2	1	1	NP	0
Riggs <i>et al.</i> ^{(30)†}	119	3	0	0	NP	NA	117	2	0	1	NP	NA
Baron <i>et al.</i> ^{(23,37)‡}	464	20	3	0	9	7	466	30	5	4	15	9
Bonithon-Kopp <i>et al.</i> ^{(28)§}	204	4	0	NA	NA	4	212	4	1	NA	NA	4
Grant <i>et al.</i> ^{(16,25)¶}	1311	94	15	14	4	50	1332	84	7	11	8	51
Grant <i>et al.</i> ^{(16,25)¶}	1306	83	20	13	4	41	1343	92	13	14	7	45
Reid <i>et al.</i> ^{(19,26)¶}	732	46	7	14	NP	7	739	42	6	9	NP	7
Lappe <i>et al.</i> ⁽¹⁵⁾	445	17	0	6	NP	NA	288	20	2	8	NP	NA
Bonnick <i>et al.</i> ⁽²⁴⁾	282	6	2	2	NP	NA	281	3	0	0	NP	NA
Reid <i>et al.</i> ⁽²⁷⁾	216	0	0	NP	0	0	107	1	0	NP	1	0
Chailurkit <i>et al.</i> ^{(29)†}	201	0	0	0	NP	NA	196	2	0	1	NP	NA
Total	5348	277	48	49	17	109	5148	282	35	49	31	116

NP, not applicable for breast cancer as all subjects were male, or for prostate cancer as all subjects were female; NA, not available.

* Total cancer excluding non-melanoma skin cancers.

† Unpublished trial-level data on reasons for study withdrawals provided by author.

‡ Unpublished trial-level data on total cancers, breast cancers and cancer-related mortality provided by the author, data on colorectal cancers and prostate cancers from published data.

§ Unpublished trial-level data on cancer deaths provided by the author, data on colorectal cancers from published data.

¶ Ca v. placebo arms in the Randomised Evaluation of Calcium Or Vitamin D (RECORD) study.

‡ Ca plus vitamin D and placebo plus vitamin D arms in the RECORD study.

randomised, placebo-controlled trials of Ca supplements have examined cancer incidence as an outcome and none as a primary endpoint. In a 4-year trial of 1179 postmenopausal women, Lappe *et al.*⁽¹⁵⁾ reported a non-significant 47% reduction in total cancer risk with Ca monotherapy,

and a significant 60% reduction with Ca plus vitamin D. There was no reduction in risk with Ca plus vitamin D compared with Ca monotherapy ($P=0.46$), suggesting that Ca supplements were responsible for the protective effects. We were unable to confirm reductions in cancer risk with

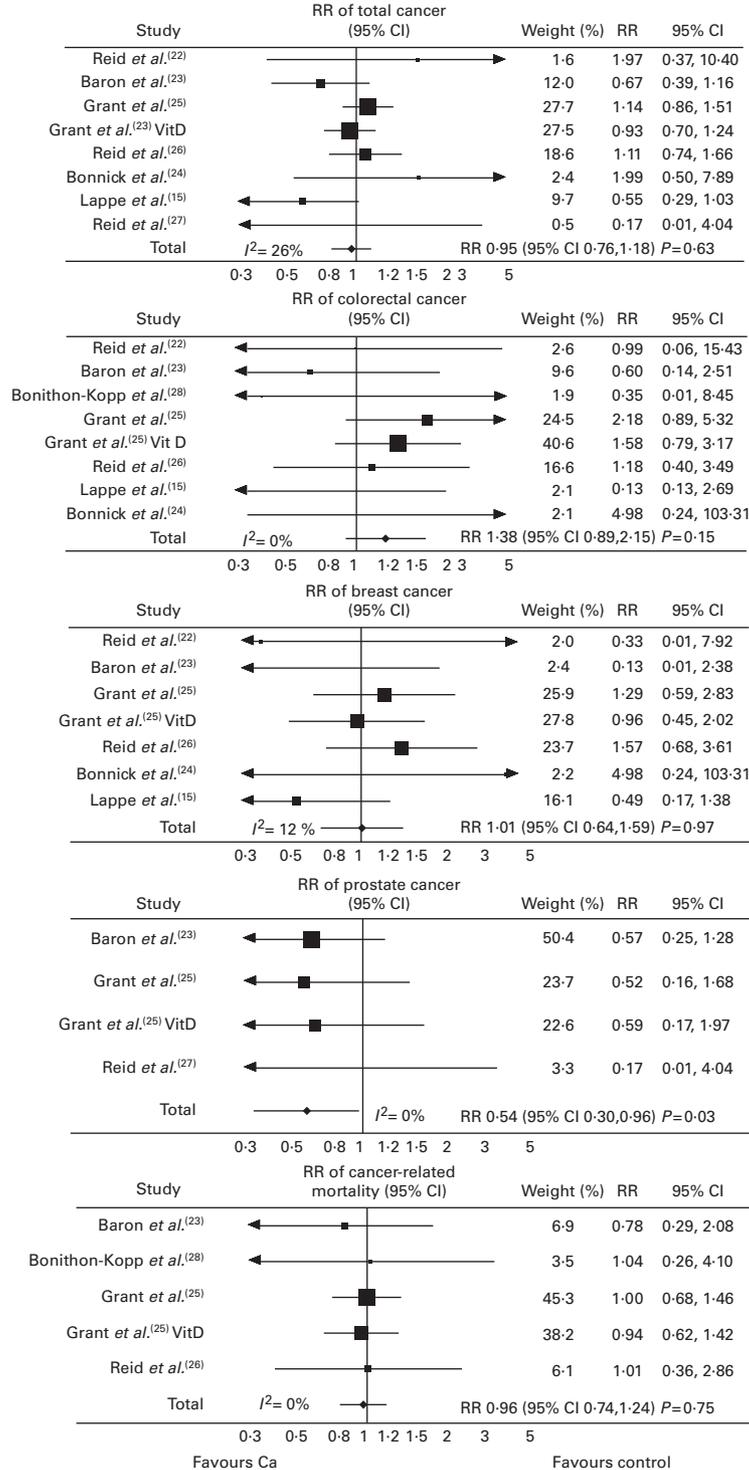


Fig. 2. Random-effects models of calcium supplementation on cancer events and cancer mortality. Full trial-level data were available for eight studies for colorectal cancer and six studies for cancer mortality. However, some studies are not shown as no events occurred: there were no colorectal cancer events in the study by Reid *et al.*⁽²⁷⁾ and was no cancer-related mortality in the study by Reid *et al.*⁽²²⁾ or Reid *et al.*⁽²⁷⁾. Grant *et al.*⁽²⁵⁾ is the calcium v. placebo arms of this study, and Grant *et al.*⁽²⁵⁾ vitamin D (VitD) is the calcium plus VitD v. VitD-only arms. RR, relative risk.

Table 4. Baseline characteristics of participants in four studies included in the patient-level analysis by treatment allocation

(Mean values and standard deviations; medians and interquartile ranges; percentages)

Characteristics	Ca group (n 3633)		Placebo group (n 3588)	
	Mean	SD	Mean	SD
Age (years)				
Median	75.2		75.6	
Interquartile range	72–80		72–80	
Women (%)*	83.0		85.6	
Caucasian (%)	99.1		99.4	
Weight (kg)	66.5	12.9	66.2	12.7
Dietary Ca (mg/d)	830	366	827	362
25-Hydroxyvitamin D (nmol/l)†	63.6	28.8	60.7	28.0
Current smoker (%)	9.9		9.1	

* Proportion of women was significantly higher in the placebo group because one study that only involved men had a 2:1 ratio of allocation to Ca or placebo. No other differences existed between groups.

† Data available from four studies for 1050 participants in the Ca group and 952 participants in the placebo group.

Ca monotherapy over an equivalent 4-year period in the present meta-analysis, with consistent findings in both trial- and patient-level analyses. Compared with the Lappe trial, the population in the present meta-analysis was older (72 *v.* 67 years), but had a lower annualised incidence of cancer in the control group (1.4 *v.* 1.7%), suggesting that the positive findings in the Lappe trial might have resulted from an unexplained high rate of cancer in the control group⁽³⁸⁾, and a small number of total cancer events (*n* 50, compared with 550 in the present meta-analysis). It is also possible that the Lappe trial results are an outlying result that might have arisen by chance.

Consistent with the present meta-analysis, a recent analysis of the RECORD study⁽¹⁶⁾, a trial of 5292 older people randomised to Ca, vitamin D, Ca with vitamin D or

placebo for a median duration of 45 months and followed for a further 3 years, found no effect of Ca (with or without vitamin D) on the risk of total cancer incidence or cancer-related mortality.

A protective effect of Ca with vitamin D supplements against total cancer, breast cancer and possibly colorectal cancer was suggested in a recent reanalysis of WHI data⁽²⁰⁾. As Ca and vitamin D were administered together in that trial, it was not possible to determine which agent was responsible for the protective effects. The results of the present meta-analysis suggest that Ca supplements for 4 years without co-administered vitamin D have no effect on the risk of total cancer, which might indicate that vitamin D, or a combination of both agents, was responsible for the observed reduction in risk in the WHI reanalysis. However, it is also possible that the present meta-analysis lacked sufficient power and/or was of too short duration to detect a small effect of Ca on total cancer risk, though the beneficial trends in the WHI were apparent from year 2. The total cancer endpoint in the WHI reanalysis was based on 1300 cancer events over 7 years among 15 600 women, whereas in the present meta-analysis, there were 550 cancer events over 4 years among 10 500 men and women. The lack of an effect of Ca on total cancer in the present meta-analysis suggests that if Ca does have an effect on total cancer risk, it is small. Future trials should use estimates from these meta-analyses to calculate sample sizes: such trials will need to be large and of a long duration. The design of such trials is discussed in detail in the description of a large trial of vitamin D and *n*-3 for cancer and cardiovascular prevention⁽³⁹⁾.

In contrast with earlier observational studies^(1–3) and colorectal adenoma chemoprevention trials^(23,40), we found no evidence that Ca monotherapy reduces colorectal cancer risk. This may have been due to the duration of the trials: if colorectal cancer has a latency period of 10–20 years,

Table 5. Results of the patient-level analysis† (Hazard ratios and 95% confidence intervals)

	Ca (n 3633)	Placebo (n 3588)	Hazard ratio	95% CI	<i>P</i>
Total events					
Total cancer	227	221	1.07	0.89, 1.28	0.50
Colorectal cancer	43	27	1.63	1.01, 2.64	0.046*
Breast cancer	41	35	1.27	0.81, 2.02	0.30
Prostate cancer	8	16	0.49	0.21, 1.14	0.10
Cancer-related mortality	98	103	0.98	0.74, 1.29	0.86
1-year latent period‡					
Total cancer	172	160	1.12	0.90, 1.39	0.30
Colorectal cancer	34	19	1.84	1.05, 3.22	0.03*
Breast cancer	33	25	1.47	0.86, 2.51	0.15
Prostate cancer	4	11	0.34	0.11, 1.08	0.07
Cancer-related mortality	77	75	1.05	0.77, 1.45	0.75
2-year latent period§					
Total cancer	112	96	1.24	0.94, 1.63	0.13
Colorectal cancer	19	14	1.39	0.70, 2.77	0.35
Breast cancer	22	17	1.51	0.78, 2.90	0.22
Prostate cancer	3	4	0.74	0.17, 3.31	0.69
Cancer-related mortality	49	42	1.2	0.79, 1.81	0.39

* *P* < 0.05.

† Number of people with cancer events.

‡ Events during the first year censored.

§ Events during the first and second year censored.

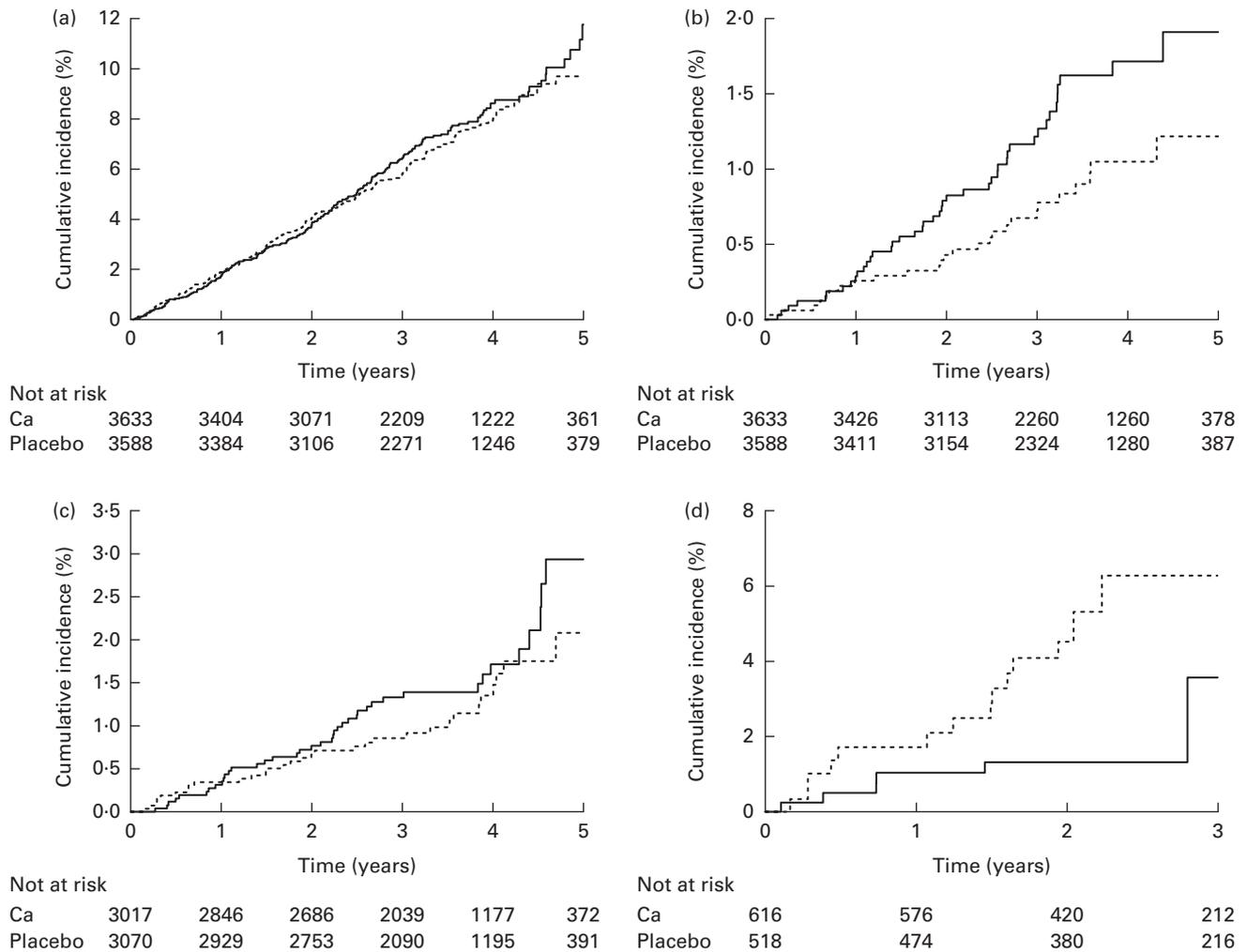


Fig. 3. Cumulative incidence of (a) total cancer (hazard ratio (HR) 1.07, 95% CI 0.89, 1.28, $P=0.50$), (b) colorectal cancer (HR 1.63, 95% CI 1.01, 2.64, $P=0.046$), (c) breast cancer (HR 1.27, 95% CI 0.81, 2.02, $P=0.30$) and (d) prostate cancer (HR 0.49, 95% CI 0.21, 1.14, $P=0.098$) in four studies that contributed patient-level data. —, Ca; - - -, placebo.

participants diagnosed during each trial may have had early-stage cancer that was present but asymptomatic and undetected at baseline. While Ca may inhibit colorectal cancer initiation, such as adenoma formation⁽²³⁾, little research has examined its effects on cancer progression. In polyp-bearing participants, Ca and antioxidants had no effect on existing adenoma growth, but significantly reduced new adenoma development over 3 years⁽⁴⁰⁾. The present meta-analysis included two trials that had participants with a history of colorectal adenoma. Because of the small number of colorectal cancer events in these trials (three in the combined Ca groups and six in the combined control groups), we were unable to investigate whether the effect of Ca on colorectal cancer was different in these participants.

We found some evidence of increased colorectal cancer risk with Ca, although this was only statistically significant in the patient-level analysis. The increased risk may have resulted from increased screening for colorectal cancer in the group allocated to Ca, as a change in bowel habits is an early

symptom of colorectal cancer⁽⁴¹⁾, and Ca supplements cause gastrointestinal side effects^(26,42). While the increased risk could reflect an effect of Ca on colorectal cancer progression, the small number of colorectal cancer events and the lack of statistical significance in the primary trial-level analysis suggest that it might be a chance finding.

We observed a reduction in prostate cancer risk with Ca in the primary trial-level analysis, largely based on two trials^(25,37) (in a third trial, only one prostate cancer event occurred⁽²⁷⁾). The risk estimate derived from the patient-level analysis was similar, although not statistically significant, probably because there were 50% fewer events than in the trial-level analysis. In a more detailed analysis of one of these trials⁽³⁷⁾, Ca had no effect on prostate cancer risk over 10 years (4 years of treatment and 6 years of post-treatment follow-up), but reduced risk by 48% during the first 6 years. These results suggest that the positive association between Ca intake and increased prostate cancer risk, suggested by some⁽⁶⁻⁸⁾ but not all^(12,13) observational studies, may be unrelated to Ca, and instead

due to other factors correlated with Ca intake, such as dairy product intake, or may have occurred from residual confounding. The small number of prostate cancer events means that the present findings should be interpreted cautiously, but if Ca does protect against prostate cancer, this could be mediated through the Ca-sensing receptor, found on prostate cells⁽⁴³⁾, or indirectly through parathyroid hormone, which has been implicated in prostate carcinogenesis⁽⁴⁴⁾.

The present meta-analysis has some limitations. Cancer was not a primary outcome of any included study, and cancer events were not collected in a standardised manner. However, unless there was a differential misclassification or misreporting of cancer events in people allocated to Ca (as we suggested for colorectal cancer), this should not have affected the present results. No data for cancer events were available for six trials comprising 20% of participants. With one exception, these trials were small, and the consistency of the findings suggests that the addition of these trials would not have affected the present results.

In summary, we found no evidence that Ca supplements without co-administered vitamin D influence total cancer risk over 4 years. The differences between the findings of the present meta-analysis and those of a recent reanalysis of the WHI, suggesting the benefits of co-administered Ca and vitamin D on cancer incidence, might be attributable to the co-administration of vitamin D in that trial. However, we cannot rule out that the present meta-analysis lacked sufficient power or that the duration of trials was too short to detect a small effect of Ca supplements. Any future trials of Ca supplements on cancer incidence should base sample size calculations on the effect sizes observed here. Such trials will need to be very large and of a long duration.

Acknowledgements

The present meta-analysis was supported by the Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation. S. M. B. is the recipient of a University of Auckland Doctoral Scholarship. M. J. B. is the recipient of a Sir Charles Hercus Health Research Fellowship. The Health Services Research Unit, University of Aberdeen, is funded by the Chief Scientist Office of the Scottish Government Health Directorates. The UK Medical Research Council funded the central organisation of the RECORD trial (grant no. G9706483).

The authors' responsibilities were as follows: S. M. B., M. J. B., A. A. and I. R. R. designed the research; S. M. B. and G. D. G. analysed the data; S. M. B., M. J. B., G. S. M., A. A., A. G. and I. R. R. wrote the manuscript; S. M. B. had primary responsibility for the content. All of the authors had access to the data and read and approved the final manuscript.

I. R. R. had study medications for clinical trials of Ca supplementation supplied by Mission Pharmacal and received research support from and acted as a consultant for Fonterra. A. A. and G. S. M. had study medications for the RECORD trial supplied by Shire Pharmaceuticals Group and Nycomed AS. None of the other authors has any conflicts of interest to declare.

References

- Garland C, Shekelle RB, Barrett-Connor E, *et al.* (1985) Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* **i**, 307–309.
- Kampman E, Slattery ML, Caan B, *et al.* (2000) Calcium, vitamin D, sunshine exposure, dairy products and colon cancer risk (United States). *Cancer Causes Control* **11**, 459–466.
- Wu K, Willett WC, Fuchs CS, *et al.* (2002) Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* **94**, 437–446.
- Shin MH, Holmes MD, Hankinson SE, *et al.* (2002) Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst* **94**, 1301–1311.
- McCullough ML, Rodriguez C, Diver WR, *et al.* (2005) Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev* **14**, 2898–2904.
- Giovannucci E, Rimm EB, Wolk A, *et al.* (1998) Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* **58**, 442–447.
- Chan JM, Giovannucci E, Andersson SO, *et al.* (1998) Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). *Cancer Causes Control* **9**, 559–566.
- Chan JM, Stampfer MJ, Ma J, *et al.* (2001) Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. *Am J Clin Nutr* **74**, 549–554.
- Kearney J, Giovannucci E, Rimm EB, *et al.* (1996) Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Am J Epidemiol* **143**, 907–917.
- Martinez ME, Giovannucci EL, Colditz GA, *et al.* (1996) Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J Natl Cancer Inst* **88**, 1375–1382.
- Larsson SC, Bergkvist L & Wolk A (2009) Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. *Am J Clin Nutr* **89**, 277–282.
- Park SY, Murphy SP, Wilkens LR, *et al.* (2007) Calcium, vitamin D, and dairy product intake and prostate cancer risk: the Multiethnic Cohort Study. *Am J Epidemiol* **166**, 1259–1269.
- Park Y, Mitrou PN, Kipnis V, *et al.* (2007) Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol* **166**, 1270–1279.
- Anderson L, Cotterchio M, Vieth R, *et al.* (2010) Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. *Am J Clin Nutr* **91**, 1699–1707.
- Lappe JM, Travers-Gustafson D, Davies KM, *et al.* (2007) Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* **85**, 1586–1591.
- Avenell A, MacLennan GS, Jenkinson DJ, *et al.* (2012) Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D₃ and/or calcium (RECORD Trial). *J Clin Endocrinol Metab* **97**, 614–622.
- Chlebowski RT, Johnson KC, Kooperberg C, *et al.* (2008) Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst* **100**, 1581–1591.
- Wactawski-Wende J, Kotchen JM, Anderson GL, *et al.* (2006) Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* **354**, 684–696.

19. Bolland MJ & Reid IR (2008) Calcium supplementation and cancer incidence. *Am J Clin Nutr* **87**, 792–793 (author reply 793–794).
20. Bolland MJ, Grey A, Gamble GD, *et al.* (2011) 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* **94**, 1144–1149.
21. Bolland MJ, Avenell A, Baron JA, *et al.* (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* **341**, c3691.
22. Reid IR, Ames RW, Evans MC, *et al.* (1993) Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* **328**, 460–464.
23. Baron JA, Beach M, Mandel JS, *et al.* (1999) Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* **340**, 101–107.
24. Bonnick S, Broy S, Kaiser F, *et al.* (2007) Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. *Curr Med Res Opin* **23**, 1341–1349.
25. Grant AM, Avenell A, Campbell MK, *et al.* (2005) Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* **365**, 1621–1628.
26. Reid IR, Mason B, Horne A, *et al.* (2006) Randomized controlled trial of calcium in healthy older women. *Am J Med* **119**, 777–785.
27. Reid IR, Ames R, Mason B, *et al.* (2008) Randomized controlled trial of calcium supplementation in healthy, non-osteoporotic, older men. *Arch Intern Med* **168**, 2276–2282.
28. Bonithon-Kopp C, Kronborg O, Giacosa A, *et al.* (2000) Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* **356**, 1300–1306.
29. Chailurkit LO, Saetung S, Thakkinstian A, *et al.* (2010) Discrepant influence of vitamin D status on parathyroid hormone and bone mass after two years of calcium supplementation. *Clin Endocrinol (Oxf)* **73**, 167–172.
30. Riggs BL, O'Fallon WM, Muhs J, *et al.* (1998) Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res* **13**, 168–174.
31. Peacock M, Liu G, Carey M, *et al.* (2000) Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab* **85**, 3011–3019.
32. Smith EL, Gilligan C, Smith PE, *et al.* (1989) Calcium supplementation and bone loss in middle-aged women. *Am J Clin Nutr* **50**, 833–842.
33. Elders PJ, Netelenbos JC, Lips P, *et al.* (1991) Calcium supplementation reduces vertebral bone loss in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age. *J Clin Endocrinol Metab* **73**, 533–540.
34. Recker RR, Hinders S, Davies KM, *et al.* (1996) Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* **11**, 1961–1966.
35. Prince RL, Devine A, Dhaliwal SS, *et al.* (2006) Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med* **166**, 869–875.
36. Dawson-Hughes B, Dallal GE, Krall EA, *et al.* (1990) A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* **323**, 878–883.
37. Baron JA, Beach M, Wallace K, *et al.* (2005) Risk of prostate cancer in a randomized clinical trial of calcium supplementation. *Cancer Epidemiol Biomarkers Prev* **14**, 586–589.
38. Schabas R (2008) Artifact in the control group undermines the conclusions of a vitamin D and cancer study. *Am J Clin Nutr* **87**, 792 (author reply 793–794).
39. Manson JE, Bassuk SS, Lee IM, *et al.* (2012) The VITamin D and Omega-3 Trial (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* **33**, 159–171.
40. Hofstad B, Almendingen K, Vatn M, *et al.* (1998) Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. *Digestion* **59**, 148–156.
41. Majumdar SR, Fletcher RH & Evans AT (1999) How does colorectal cancer present? Symptoms, duration, and clues to location. *Am J Gastroenterol* **94**, 3039–3045.
42. Lewis JR, Zhu K & Prince RL (2011) Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res* **27**, 719–722.
43. Sanders JL, Chattopadhyay N, Kifor O, *et al.* (2001) Ca(2+)-sensing receptor expression and PTHrP secretion in PC-3 human prostate cancer cells. *Am J Physiol Endocrinol Metab* **281**, E1267–E1274.
44. Ritchie CK, Thomas KG, Andrews LR, *et al.* (1997) Effects of the calcitrophic peptides calcitonin and parathyroid hormone on prostate cancer growth and chemotaxis. *Prostate* **30**, 183–187.