Calcium Intake and Colorectal Cancer Risk: Dose-Response Meta-Analysis of Prospective Observational studies

NaNa Keum,[1] MS; Dagfinn Aune,[2,3] MS; Darren C Greenwood,[4] PhD; Woong Ju,[5] MD; Edward L Giovannucci,[1,6] ScD

1. Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, USA
2. Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
3. Department of Epidemiology and Biostatistics, Imperial College London, London, UK
4. Division of Biostatistics, University of Leeds, Leeds, UK
5. Department of Obstetrics and Gynecology, Ewha Womans University, Seoul, Republic of Korea
6. Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, USA

Running title:
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Corresponding author:
NaNa Keum
Departments of Nutrition and Epidemiology
Harvard School of Public Health
Building 2, 3rd Floor
655 Huntington Avenue, Boston, MA, 02115, USA
Phone: 617-432-4648
Fax: 617-432-2435
E-mail: nak212@mail.harvard.edu

Keywords:
dietary calcium; calcium supplements; colorectal cancer; meta-analysis; dose-response

Article category:
Research article under Epidemiology

Word count for the main text: 4,544
Count of tables and figures: 5
Reference count: 51

Novelty and Impact Statements
This is the first dose-response meta-analysis that identified the shape of relationship between calcium intake and colorectal cancer risk, by sources of calcium. By showing an equivalent benefit of dietary and supplementary calcium for the prevention of colorectal cancer, this manuscript supports for diversifying sources of calcium intake into supplements and non-dairy products fortified with calcium, which could benefit people with lactose intolerance or low dairy consumption for the prevention of colorectal cancer.

Abstract

Mechanistic and epidemiologic studies provide considerable evidence for a protective association between calcium intake and incident colorectal cancer (CRC). While the relationship has not been substantiated by short-duration randomized controlled trials (RCTs) of CRC, trials do show a benefit on adenomas, a precursor to CRC. To address some of this inconsistency, we conducted dose-response meta-analyses by sources of calcium intake, based on prospective observational studies published up to December 2013 identified from PubMed, Embase, and BIOSIS. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model. For total calcium intake, each 300mg/day increase was associated with an approximately 8% reduced risk of CRC (summary RR=0.92, 95% CI=0.89-0.95, I^2=47%, 15 studies with 12,305 cases, intake=250-1900 mg/day, follow-up=3.3-16 years). While the risk decreased less steeply in higher range of total calcium intake ($P_{non\text{-}linearity}$=0.04), the degree of curvature was mild and statistical significance of non-linearity was sensitive to one study. For supplementary calcium, each 300mg/day increase was associated with an approximately 9% reduced risk of CRC (summary RR=0.91, 95% CI=0.86-0.98, I^2=67%, six studies with 8,839 cases, intake=0-1150 mg/day, follow-up=5-10 years). The test for non-linearity was not statistically significant ($P_{non\text{-}linearity}$=0.11). In conclusion, both dietary and supplementary calcium intake may continue to decrease CRC risk beyond 1000mg/day. Calcium supplements and non-dairy products fortified with calcium may serve as additional targets in the prevention of CRC. RCTs of calcium supplements with at least 10 years of follow-up are warranted to confirm a benefit of calcium supplements on CRC risk.

Introduction

Considerable evidence suggests that milk intake may decrease the risk of CRC,[1, 2] which is the third most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide.[3] Possible protective nutrients in milk include calcium,[4-7] vitamin D if milk is fortified,[8, 9] and some fat components such as conjugated linoleic acid[10] and butyric acid.[11] Due to the high calcium content in milk, calcium is thought to be the major nutrient that mediates the beneficial effect of milk on CRC. The involvement of calcium in the etiology of CRC is supported by several biological mechanisms. Garland et al. first hypothesized that intracelluar calcium in the colonic epithelial cells may reduce the cancer-promoting inflammatory response to bacterial flora and other agents in the colonic lumen.[12] Experimental studies in animals and humans suggest that calcium may bind secondary bile acids or ionized fatty acids in the colorectal lumen, diminishing their carcinogenic effects on the colorectal mucosa.[4, 5] Alternatively, evidence from in vivo and in vitro human colonic epithelial cells suggests that calcium may reduce cell proliferation and promote cell differentiation by modulating cell signaling.[6, 7] In a RCT, calcium supplementation of 2000 mg/day induced favorable changes on gene expression in the APC/β-catenin pathway in the normal mucosa of colorectal adenoma patients.[13] Perturbations of this pathway is a common early event in colorectal carcinogenesis.

Despite such biological plausibility, epidemiologic studies and RCTs have found inconsistent results. While a meta-analysis[14] and a pooled analysis[2] of observational studies found a statistically significant protective association, a recent meta-analysis of eight RCTs showed that assignment to calcium supplements without co-administered vitamin D did not statistically significantly alter the CRC risk.[15] Due to the lack of strong evidence from calcium supplement trials, in *The Colorectal Cancer 2011 Report* from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), calcium was classified as a probable protective factor of CRC rather than a convincing one.[16]

Several explanations could account for the apparent discrepancy. Possibly, calcium is not the causal factor, and thus it is important to consider if another nutrient in milk, particularly vitamin D, may account for the association. Also important to determine from the observational studies is whether calcium from supplements is similarly associated with lower risk of CRC as calcium from foods, particularly given that all the trials tested only supplementary calcium, and dietary and supplementary calcium might differ in bioavailability.[17] Alternatively, the lack of a statistically significant finding in the meta-analysis of trials might have resulted from several methodological limitations of trials such as short follow-up period and inadequately addressed dose-response relationship. To address some of these issues, we conducted a dose-response meta-analysis of prospective observational studies that aims to characterize the shape of the relationship between calcium intake and CRC risk, examined the association by dietary and supplementary sources of calcium, and carefully considered the potential role for confounding, particularly by dietary vitamin D.

Methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was followed for the design, analysis, and reporting of this meta-analysis.[18] Two authors (NK and WJ) participated in literature search, study selection, and data extraction independently. Inconsistency between researchers was resolved through discussion.

Literature Search

A literature search was performed based on PubMed, Embase, and BIOSIS databases for studies published up to December 2013. Detailed search terms are provided in the online supplementary method. The language was limited to English and no other restrictions were imposed. Abstracts and unpublished results were not included. The reference lists of selected systematic reviews and meta-analyses, and all the articles included in our analysis were also reviewed for additional papers.

Study Selection

To be included, studies had to be a prospective observational study (cohort studies analyzed with nested case-control, case-cohort, or prospective cohort approaches) investigating the relationship between calcium intake and incident cancer of the colon or rectum; providing a quantitative measure of calcium intake for at least 3 categories with the estimates of RRs (hazard ratio or risk ratio), 95% confidence interval (CI), category-specific or total number of cases, and category-specific or total number of either person-years or noncases. Retrospective studies were excluded to minimize recall and selection bias. When there were several publications from the same cohort, the publication with the largest number of cases was selected. This process of study selection and reasons for exclusion are summarized in Figure 1. Authors of three publications[2, 19, 20] were contacted for additional information (e.g. category-specific cases, category-specific person-years) and they all provided the requested data. A total of 21 publications were included to extract data for 20 prospective observational studies.

Data Extraction

From each study, the following information was extracted: Category-specific dose of calcium intake (range, mean, or median), the most fully adjusted RRs and their 95% CIs, the first author's last name, publication year, study design, study name, country of the study cohort, exclusion criteria, sex, age at baseline, sample size, number of cases, follow-up period, number of person-years, types of calcium intake (total=dietary+supplementary, dietary, supplementary), types of CRC (CRC, colon cancer (CC), rectal cancer (RC)), dietary assessment method (type, whether it had been validated), number of dietary measurements (baseline only, updated), outcome ascertainment method, variables adjusted for, variables reported to be not adjusted for based on the statistical criteria, reverse causation (whether it was addressed, whether sensitivity analysis excluding cases during the first few years follow-up changed the results substantially).

Statistical Analysis

For the linear dose-response analysis assuming a linear relationship between calcium intake and CRC risk, the method described by Greenland and Longnecker[21] was used to calculate study-specific RRs (linear slopes) and 95% CIs from the natural logs of extracted RRs and 95% CIs across categories of calcium intake. Study-specific RRs and variance/covariance matrices were pooled using a random effects model to calculate the summary RR and 95% CI. This method for linear dose-response analysis requires that the distribution of cases, the distribution of person-years or noncases, and RRs with the variance estimates are known for at least 3 quantitative exposure categories. When studies did not provide distributions of cases or person-years, authors were contacted or approximations were made if possible (e.g., if studies analyzed calcium intake by quartiles, the category-specific number of person-years was estimated by dividing the total number of person-years by 4). For studies that showed results separately for colon and rectal cancer or for men and women, category-specific RRs and variances were combined using a fixed effects model with inverse variance weight to obtain combined estimates for CRC or for both sexes, before calculating study-specific RRs and CIs. In each study, the mean or median value of calcium intake in each category was assigned to the corresponding RR. When the lowest or highest categories were open-ended, the length of the open-ended interval was assumed to be the same as that of the adjacent interval. Calcium intakes reported in densities (mg/kcal) were converted into absolute intakes (mg/day) using the mean or median energy intake of the study population. Forest plots of the linear dose-response results are presented for RRs for a 300mg daily increment of calcium intake (equivalent to calcium content in one serving (250 mL) of milk).

To examine a potential non-linear relationship between calcium intake and CRC risk, fractional polynomial models were used.[22] The best-fitting second order fractional polynomial model was determined as the one with the lowest deviance. The linear and non-linear models were compared using a likelihood test to test for non-linearity.

Heterogeneity in the relationship between calcium intake and CRC across studies was assessed by Q test and quantified by I^2.[23] To identify sources of heterogeneity, subgroup analyses and meta-regression were conducted based on *a priori* selected variables related to etiologic heterogeneity and potential effect modifiers. To assess study quality, subgroup analyses and meta-regression were conducted by variables concerning methodological characteristics. Potential for small study effects, such as publication bias, was assessed using Egger's test[24] and Begg's test.[25] Diverse sensitivity analyses including the influence analysis were performed to explore robustness of the results.

For statistical significance, two-sided α was set at P=0.05. All statistical analyses were conducted using STATA 12 (StataCorp, College Station, TX).

Results

Overall calcium intake: primary analysis

While total calcium intake is the exposure measure from which the best dose-response relationship between calcium intake and CRC risk could be inferred, not all studies have information on supplementary calcium intake, limiting their investigation only to the effect of dietary calcium intake. Since total calcium intake is reasonably approximated by dietary calcium intake if the prevalence of calcium supplement use is low (<5%) in the study cohort, our primary analyses included studies that reported total calcium intake and studies that only examined dietary calcium intake but their cohorts have a low prevalence of calcium supplement use.

Fifteen cohort studies[19, 26-39] were included in the primary dose-response meta-analysis of calcium intake (10 total, 5 dietary) and CRC risk (12 CRC, 3 CC), providing a total of 12,305 cases among 1,415,597 participants with mean total calcium intake ranging approximately between 250 to 1900 mg/day (Table 1). From the linear dose-response analysis, the summary RR for a 300 mg/day increase in total calcium intake was 0.92 (95% CI=0.89-0.95), with moderate heterogeneity (I^2=47%, $P_{heterogeneity}$=0.02) (Figure 2A). Small study effects, such as publication bias, were not evident (P_{Egger}=0.34, P_{Begg}=0.73). In sensitivity analyses omitting one study at a time, the results were not influenced greatly by any of the studies. In other sensitivity analyses such as excluding studies[19, 28] that used CC as the outcome and replacing 3 cohort studies[19, 26, 39] included in the pooling project[2] with the pooling project itself, the results did not change materially (data not shown).

Slight non-linearity was apparent, with CRC risk decreasing more steeply in lower range of total calcium intake than in higher range ($P_{non\text{-}linearity}$=0.04) (Figure 3). Albeit statistically significant, the degree of curvature was mild. Compared to 250 mg/day of total calcium intake, the summary RR was 0.82 (95% CI=0.71-0.95) at 1000 mg/day and further reduced to 0.74 (95% CI=0.65-0.85) at 1750 mg/day. However, the scatter plot suggested that the decreasing rate of reduction in CRC risk with increasing total calcium intake may be strongly driven by the study by Jarvinen et al.,[35] which reported a statistically non-significantly increased risk of CRC at the highest total calcium intake observed. When excluding this study, the dose-response curve showed no evidence of non-linearity ($P_{non\text{-}linearity}$=0.08).

As a sensitivity analysis aiming to derive the calcium and CRC relationship from the most inclusive data, we repeated the same linear and non-linear dose-response meta-analyses in 20 studies[19, 20, 26-43] that reported total (n=10) or dietary (n=10) calcium intake (Table 1). Results did not change materially (data not shown).

Overall calcium intake: secondary analysis

In order to further investigate if the dose-response relationship between total calcium intake and CRC risk differs by supplementary calcium use, the primary dataset including 15 studies (10 total, 5 dietary)[19, 26-39] was divided into the following two subsets.

1) Subset representing populations with an appreciable use of calcium supplements

Ten cohort studies[19, 26-33, 39] that reported total calcium intake including supplementary calcium were included (10,601 cases, 1,186,722 participants, range=250-1700 mg/day) (Table 1). In the linear dose-response analysis, the summary RR for a 300 mg/day increase was 0.93 (95% CI=0.89-0.96) with moderate heterogeneity (I^2=53%, $P_{heterogeneity}$=0.02) (Figure 2B). Small study effects such as publication bias were not evident (P_{Egger}=0.44, P_{Begg}=0.92). In sensitivity analyses such as omitting one study at a time, excluding studies[19, 28] that used CC as the outcome, and replacing three cohort studies[19, 26, 39] included in the pooling project[2] with the pooling project itself, the results did not change materially (data not shown). The test for non-linearity was not statistically significant ($P_{non\text{-}linearity}$=0.11).

2) Subset representing populations with a low use of calcium supplements

The remaining five studies[34-38] reporting dietary calcium intake were included. Of note, three studies[19, 33] that reported total calcium intake also provided estimates for the effect of dietary calcium intake on CRC risk among non-supplement users. Thus, a total of eight studies[19, 33-38] were included in this subgroup (3,770 cases, 451,568 participants, range of intake=250-1900 mg/day) (Table 1). In the linear dose-response analysis, the summary RR for a 300 mg/day increase was 0.90 (95% CI=0.85-0.96, I^2=27%, $P_{heterogeneity}$=0.21) (Figure 2C). Small study effects such as publication bias were not evident (P_{Egger}=0.98, P_{Begg}=1.00). In sensitivity analyses such as omitting one study at a time and excluding studies[19] that used CC as the outcome, the results did not change materially (data not shown). The test for non-linearity was not statistically significant ($P_{non\text{-}linearity}$=0.07).

Supplementary calcium intake: primary analysis

The presence of a relatively high number of calcium supplement users in the U.S. provided an opportunity to investigate the dose-response association of supplementary calcium intake with CRC risk. Six cohort studies[26, 27, 30-33] from the U.S. were included (5 CRC, 1 CC), providing a total of 8,839 cases among 920,837 participants with mean supplementary calcium intake ranging approximately between 0 to 1150 mg/day (Table 1). In the linear dose-response analysis, the summary RR for a 300 mg/day increase was 0.91 (95% CI=0.86-0.98), with moderate heterogeneity (I^2=67%, $P_{heterogeneity}$ =0.01) (Figure 2D). Small study effects such as publication bias were not evident (P_{Egger}=0.43, P_{Begg}=0.85). In sensitivity analyses omitting one study at a time, the results were not influenced greatly by any of the studies. The test for non-linearity was not statistically significant ($P_{non\text{-}linearity}$=0.11).

Supplementary calcium intake: secondary analysis

To examine indirectly if supplementary and dietary calcium form differential relationships with CRC risk, six studies[26, 27, 30-33] were identified that provided results in the entire population regarding both total and dietary calcium intake (Table 1). Adding supplementary calcium intake on top of background dietary calcium intake did not change the

linear dose-response relationship, as the summary RR for a 300 mg/day increase was similar between total calcium (0.93, 95% CI=0.89-0.97, I^2=62%, $P_{heterogeneity}$ =0.02, range of intake=350-1700 mg/day) and dietary calcium (0.92, 95% CI=0.90-0.95, I^2=0%, $P_{heterogeneity}$=0.85, range of intake=300 to 1200 mg/day). Both estimates were free of small study effects, such as publication bias, and robust to the influence of any single study (data not shown).

Subgroup analyses

While extensive subgroup analyses were done for total calcium intake, only sex-specific subgroup analyses were conducted for supplementary calcium intake due to the limited number of studies available (Table 2). In investigating potential etiologic heterogeneity between CC and RC, there was no evidence of heterogeneity between subsites, but statistical significance of an inverse association was limited to CC. In exploring heterogeneity by potential effect modifiers and by methodological characteristics, there was no evidence of between-subgroup heterogeneity. A statistically significant inverse association was observed in most subgroups. In some subgroups with a statistically marginally-significant inverse association, exclusion of the study by Jarvinen et al.[35] improved statistical significance and reduced within-subgroup heterogeneity.

Discussion

Our linear dose-response analysis supports an approximately 8% decreased risk of CRC associated with a 300 mg/day increase in calcium intake, which holds for both dietary and supplementary calcium, for both men and women, and more consistently for CC than for RC. While there was statistically significant evidence for a non-linear relationship with CRC risk decreasing less steeply at higher total calcium intake, the degree of curvature was mild suggesting that, overall, a linear association is a reasonable summary of the dose-response relationship within the observed calcium intake of 250-1900 mg/day. The statistical significance of non-linearity was further discounted because the test for non-linearity was sensitive to the presence of the study by Jarvinen et al.,[35] which was atypical in several respects; it was the only study without a validated dietary questionnaire, and it had the highest calcium intakes observed, the smallest number of cases, the youngest age range because the study recruited anyone aged 15 years or older, and the longest mean follow-up.

Limitations of the study

Combining many studies allowed us to robustly investigate calcium intake over a wide range, but the resulting heterogeneity was significant and subgroup analyses did not identify statically significant sources of between-subgroup heterogeneity. However, as suggested in the forest plots, heterogeneity was largely attributable to variations in the magnitude of RRs than to differences in the directionality of RRs. Furthermore, heterogeneity was lower in subgroups that adjusted for intake of red meat, dietary fiber, folate intake, screening, and NSAID use, when the analysis was restricted to CC, and when the analysis was stratified by gender. Excluding the study by Jarvinen et al.[35] substantially reduced heterogeneity in several subgroups. While no evidence for small study effects such as publication bias was found in this analysis, we were not able to investigate potential etiologic heterogeneity between proximal and distal CC associated with calcium intake due to the selective reporting of results on subsite-specific CC.

Measurement error in the assessment of calcium intake is of concern because it could have affected the magnitude and shape of the dose-response relationship between calcium intake and CRC risk. Meta-analysis is inevitably prone to any measurement error in the studies included. While most of the included studies used validated dietary questionnaires whose ability to assess relative calcium intake was tested to be reasonable, such questionnaires do not necessarily ensure their validity to measure absolute calcium intake, on which dose-response meta-analysis relied. Thus, measurement errors in assessing absolute calcium intake within each study compromise the validity of our quantitative findings. Further measurement error is introduced in the procedure of meta-analysis, as the investigation of the dose-response relationship based on results provided for a categorical calcium intake necessitates some assumptions. For instance, assigning mean or medium calcium intake of a category to the corresponding RR, assigning the length of the adjacent interval to an open-ended lowest or highest category, and converting calcium intake reported in density to absolute intake (mg/day)

using the mean or median energy intake of the study population, are all potential sources of measurement error. While some robustness to measurement error is suggested by the finding that total, dietary, and supplementary calcium intake, despite having possibly different measurement errors, consistently showed an inverse linear association, we cannot completely ruled out differential effects of different measurement errors on different true RRs producing an appearance of robustness. Altogether, measurement errors from diverse sources are inevitable, and while their direction of bias cannot be predicted, they are generally anticipated to attenuate the true effect.[44] Thus, our quantification of a linear association as an approximately 8% reduced risk of CRC with a 300 mg/day increase in calcium intake may be an underestimation of the true calcium effect.

Strengths of the study

First, this analysis is based on strong biological plausibility as explained in the introduction and our findings are also supported by RCTs with adenoma endpoint, a precursor to CRC. By including 15 prospective studies, we had adequate statistical power to assess the shape of dose-response relationship over a wide range and for diverse sources of calcium intake. Since we included only prospective studies, our findings are less likely to be explained by recall and selection bias. While unmeasured or residual confounding and reverse causation are of concern, our extensive subgroup analyses showed that none of the methodological aspects was a statistically significant source of heterogeneity. Furthermore, a statistically significant association persisted in most strata that adjusted for confounders and addressed reverse causation. Since most studies had a long duration of follow-up, our meta-analysis was advantageous in mitigating the influence of reverse causation and accounting for a potential long induction period relating calcium to CRC risk.

Findings from our meta-analyses help address the critical confounding by dietary vitamin D. Considering that vitamin D has been suggested to protect against CRC[8, 9] and fortified milk is the major common source of both dietary calcium and dietary vitamin D in many countries, confounding by dietary vitamin D complicates the distinction of an effect of calcium itself from that of dietary vitamin D in epidemiologic studies. Our subgroup analyses provide three lines of evidence against confounding by dietary vitamin D. A linear inverse association between calcium intake and CRC risk remained statistically significant, first in the subgroup of studies that controlled for dietary vitamin D intake or stated no confounding from dietary vitamin D based on statistical test; second among studies conducted in countries without nationwide vitamin D fortification; third in two studies conducted in Asia (China, Japan)[34, 38] where nationwide vitamin D fortification is absent and the major food sources of dietary calcium and vitamin D are distinctive (in China, dietary calcium were mostly from non-dairy products such as vegetables and soy foods, which are not rich in vitamin D; in Japan, the major source of dietary calcium and vitamin D was milk and fish, respectively). Such presence of a statistically significant inverse association in populations where dietary vitamin D is unlikely to be

associated appreciably with dietary calcium strongly reduces the likelihood of confounding by vitamin D.

Our analyses on supplementary calcium provide an opportunity to better evaluate a protective effect of calcium on CRC risk and bioavailability by sources of calcium. In its secondary analysis, the magnitude of a linear inverse association was virtually identical regardless of whether calcium is purely from food or from mixed sources of food and supplements. This result that mixing dietary calcium with supplementary calcium did not alter the magnitude of the inverse association is consistent with the hypothesis that calcium is the major CRC-protective agent in milk and that bioavailability of calcium is similar for dietary and supplementary sources within the range of intakes studied.

Comparison with other studies

Our results are broadly consistent with two previously published studies, a meta-analysis of 60 observational studies[14] and a pooled analysis of 10 cohort studies[2] and yet provide additional information that addresses unanswered questions. While the previous meta-analysis[14] could only determine directionality of the relationship, our linear dose-response analysis further quantified that a 300 mg/day increase in calcium intake was associated with an approximately 8% reduced risk of CRC. In the pooled analysis,[2] a nonparametric regression analysis indicated a non-linear relationship with little further reduction in CRC risk at a total calcium intake beyond 1000mg/day. Yet, it had relatively sparse data to evaluate statistical significance of the non-linearity. Our meta-analysis with more than 4 times as many cases formally assessed non-linearity and showed that, despite statistical significance of non-linearity, a linear shape is a reasonable approximation as the degree of curvature was mild. In particular, since the non-linearity identified in our meta-analysis is characterized by decreasing incremental benefit of total calcium intake rather than reaching a plateau, regardless of statistical significance of the non-linearity, the risk of CRC continued to decrease within the observed range of 250-1900 mg/day of total calcium intake.

Findings from our meta-analysis may help understand the discrepant results between the observational studies and the RCTs, which were stated in the introduction. First, given the broadly linear association, the high baseline calcium intake of the participants (≥750 mg/day) in the trials might not explain the null finding of the trials. Second, the similar magnitude of a linear association observed regardless of sources of calcium intake argues against attributing differential bioavailability between dietary and supplementary calcium to the trials' null finding within the range of intakes observed. Third, while causality cannot be proven, our consistent finding of a linear association across total, dietary, and supplementary calcium intake, the presence of dose-response relationship, and evidence against confounding by dietary vitamin D increase our confidence regarding a true beneficial effect of calcium on CRC risk. Further considering that the confidence interval for the meta-analysis of eight trials was wide (summary RR=1.38, 95% CI=0.89-2.15),[15] it may be difficult to rule out a true causal effect of calcium on CRC. For the aforementioned reasons, findings from our meta-analyses point to the trials' short

duration of less than five years as the primary explanation for the lack of a statistically significant finding. Our meta-analysis was not able to directly examine the calcium-CRC relationship by duration of calcium use. Yet, since dietary habits tend to track over time, supplementary calcium intake at baseline in observational studies is likely to reflect prior supplementary calcium intake and thus to represent a long-term intake. Consistent with this hypothesis, five out of six studies included in our meta-analysis on supplementary calcium intake found a statistically significant inverse association after 5-10 years of follow-up.

Further evidence for the plausibility of detecting an effect with a long-term follow-up comes from trials that used adenoma as a surrogate endpoint of CRC. Given that the prevention or removal of an adenoma leads to the prevention of CRC and that it takes at least 10 years in general for adenoma to progress to CRC,[45] the presence of a protective effect of calcium supplementation on adenoma indicates that the effect of calcium on CRC might become evident with longer follow-up. In a recent meta-analysis of two RCTs (mean baseline dietary calcium intake=876-918 mg/day), assignment to 1200-2000 mg/day of calcium supplements alone statistically significantly reduced the recurrence of any adenoma over 3-4 years (summary RR=0.82, 95% CI=0.69-0.98, I^2=0%).[46] In one of the two trials, assignment to calcium supplementation of 1200 mg/day over 4 years conferred the strongest benefit on advanced histology neoplasm (RR=0.65, 95% CI=0.46-0.93),[47] suggesting that calcium may inhibit the formation or progression of adenomas that have a high propensity to progress to cancer.

Conclusions, clinical and public health implications, and recommendations for future studies

Higher calcium intake may be associated with a continued reduction in CRC risk beyond 1000mg/day. The inverse association was not likely explained by confounding by dietary vitamin D, and existed for both dietary and supplementary calcium. Our findings have several important clinical and public health implications. First, according to the 2003-2006 National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey in the U.S., median total calcium intake of adults aged over 50 years was approximately 650 mg/day for no calcium-supplement users and 1000 mg/day for calcium-supplement users.[48] As the benefit of calcium intake on CRC is expected to continue beyond 1000 mg/day, not only non-supplement users but also supplement users may further reduce their CRC risk through additional calcium intake. Considering that calcium intakes of the U.S. population are relatively high due to the high prevalence of supplement use, other populations with lower baseline calcium intakes are expected to achieve greater benefit through an increased calcium intake. Second, while dairy products, especially milk, are the major sources of calcium in many countries, they are a substantial source of calories and contain potentially harmful factors such as saturated fat, hormones, and casein proteins.[49-51] Since our analyses provide evidence for an equivalent benefit of dietary and supplementary calcium, the benefit of calcium on CRC risk may be obtained through supplements and non-dairy products fortified with calcium. Additional calcium from diverse sources may substantially benefit Asians in reducing CRC incidence, as

Asian populations are marked by an increasing trend in CRC incidence rates, low calcium status, and high prevalence of lactose intolerance.

Given that all the studies on calcium supplements were from the U.S., future studies should evaluate the effect of supplementary calcium intake on CRC risk in diverse populations. RCTs of calcium supplements with at least 10 years of follow-up are warranted to confirm a role of calcium supplements as a chemopreventive agent against CRC. Lastly, as diversifying sources of calcium intake has important implications, future studies should also examine if the beneficial effect of dietary calcium on CRC is modified by dairy and non-dairy sources.

Acknowledgement: We thank librarian Carol Mita for providing consultations on literature searching, Professor Eunyoung Cho, Dr. Kana Wu, and Professor Anne Zeleniuch-Jacquotte for providing requested data for this analysis, and Professor Chung-Cheng Hsieh for invaluable advice on this meta-analysis.

Conflict of Interest: Dr. Greenwood reports grants from Danone and personal fees from American Institute for Cancer Research / World Cancer Research Fund, outside the submitted work. The other authors declare none.

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Figure legends

Fig 1. Flowchart of study selection
Fig 2. Linear dose-response meta analyses on CRC risk associated with a 300mg/day increase in (A) total calcium intake, (B) total calcium intake in populations with an appreciable use of calcium supplements, (C) total calcium intake in populations with a low (<5%) use of calcium supplements, (D) supplementary calcium intake. RR=Relative Risk for a 300mg/day increase in calcium intake of each type; CI=Confidence Interval.
Fig 3. Non-linear dose-response meta-analysis on total calcium intake and CRC risk ($P_{non\text{-}linearity}$=0.04; reference: 250mg/day) RR=Relative Risk compared to 250mg/day of total calcium intake.

Tables

Table 1. Main characteristics of the studies included in the dose-response meta-analysis on calcium intake and CRC risk

First author, Year, Country, (reference)	Study name	Follow-up period	Study size, No of cases, Sex, Age at baseline	Diet assessment method, CRC ascertainment method	Type of calcium	Highest vs lowest mean/median dose (mg/day)	RR (95% CI)	Variables adjusted for/ Variables reported to be not adjusted for based on statistical test
Studies that reported total calcium intake								
Park, 2009, USA, [32]	NIH-AARP Diet and Health Study	1995-2003, 7 yrs	492810, CRC:5099, M/F, 50-71 yrs	Validated FFQ, 124 items Cancer registries	Total	1672 vs. 513	0.77 (0.69, 0.85)	Age, energy intake, sex, race, education, marital status, FH, BMI, PA, smoking, alcohol, red meat, fruits, vegetables, whole grains, folate, HRT(women), dietary calcium (supplementary) /NR
					Supplementary	1100 vs. 0	0.82 (0.71, 0.94)	
Park, 2007, USA, [33]	Multiethnic Cohort Study	1993/96-2001, 7.3 yrs	191011, CRC:2110, M/F, 45-75 yrs,	Validated FFQ, >180 items Cancer registries, Death certificates	Total	1425 vs.512	0.67 (0.55, 0.81)	Age, time since cohort entry, energy intake, sex, race, FH, history of polyps, BMI, PA, smoking, fiber, NSAID use, HRT(women), regular use of multivitamin use (total), dietary calcium(supplementary) /NR
			116133, CRC:1285		Dietary among non-users of calcium supplements	1051 vs. 475	0.72 (0.57, 0.90)	
			191011, CRC:2110		Supplementary	300 vs. 0	0.79 (0.69, 0.90)	
Larsson, 2006, Sweden, [29]	Cohort of Swedish Men	1997-2004, 6.7 yrs	45306, CRC:449, M, 45-79 yrs	Validated FFQ, 96 items Cancer registries	Total	1577 vs. 844	0.68 (0.51, 0.91)	Age, energy intake, education, FH, history of diabetes, BMI, PA, smoking, alcohol, red meat, saturated fat, fruits, vegetables, vitamin D, aspirin, multivitamin use /NR

Flood, 2005, USA, [27]	Breast Cancer Detection Demonstration Project	1987/89-1995/98), 8.5 yrs	45354, CRC:484, F, 61.9 yrs	Validated FFQ, 62 items Medical records, Cancer registries, National Death Index	Total	1676 vs. 377	0.74 (0.55, 0.99)	Age, time since program entry, energy intake(total), screening center, race /education, history of breast disease, BMI, height, PA, smoking, alcohol, meat, fat, fruits, vegetables, grains, fiber, folate, vitamin D, NSAID use, HRT, endoscopy
					Supplementary	1130 vs. 0	0.76 (0.56, 0.98)	
Lin, 2005, USA, [30]	US Women's Health Study	1993-2004, 10 yrs	36976, CRC:223, F, ≥45 yrs 36976, CRC:223,	Validated FFQ, 131 items Medical records	Total	1527 vs. 528	1.20 (0.79, 1.85)	Age, energy intake, randomized treatment assignment, FH, history of polyps, BMI, PA, smoking, alcohol, red meat, saturated fat, HRT, multivitamin use /NR
					Supplementary	750 vs. 0	1.30 (0.90, 1.87)	
McCullough, 2003, USA, [31]	CPS II Nutrition Cohort	1992/93-1997, 5 yrs	127749, CRC:683, M+F, 50-74 yrs	Validated FFQ, 68 items Medical records, Cancer registries	Total	1421 vs. 475	0.87 (0.67, 1.12)	Age, energy intake, education, FH, BMI, PA, smoking, saturated fat, fruits, vegetables, HRT(women), long-term multivitamin use /alcohol, red meat, fiber
					Supplementary	730 vs. 0	0.69 (0.49, 0.96)	
Wu, 2002, USA, [19]	Health Professionals Follow-up Study	1986-1996, 10 yrs	47344, CC:399, M, 40-75 yrs	Validated FFQ, NR Medical records	Total	1376 vs. 250	0.64 (0.43, 0.95)	Age, energy intake, FH, BMI, PA, smoking before age 30, alcohol, red meat, aspirin /total fat, fiber, iron, methionin, folate, vitamin A,C,E, and D, carotene, multivitamin use, endoscopy
			42152, CC:356		Dietary among non-users of calcium supplements	1100 vs. 250	0.67 (0.46, 0.96)	
Wu, 2002, USA, [19]	Nurses' Health Study	1980-1996, 16 yrs	87998, CC: 626, F, 30-55 yrs	Validated FFQ, NR Medical records	Total	1376 vs. 250	0.94 (0.66, 1.33)	Age, energy intake, FH, BMI, PA, smoking before age 30, alcohol, red meat, aspirin, HRT, menopausal status / total fat, fiber, iron,

			64409, CC:425		Dietary among non-users of calcium supplements	1100 vs. 250	0.97 (0.68, 1.38)	methionin, folate, vitamin A,C,E, and D, carotene, multivitamin use, endoscopy
Sellers, 1998/ Zheng, 1998,* USA, [26, 39]	Iowa Women's Health Study	1986-1994/95, 9.5 yrs	61639, CRC:385, F, 55-69 yrs	Validated FFQ, 127 items State Health registry	Total	1525 vs. 571	0.63 (0.47, 0.83)	Age, energy intake, history of polyps (Sellers), smoking(Zheng), HRT(Zheng) /NR
Sellers, 1998			26937, CC:241,		Supplementary	750 vs. 0	0.68 (0.48, 0.97)	
Gaard, 1996, Norway, [28]	Norweigian National Heatlh Screening Service	1977/83-1991, 11.4 yrs	50535, CC: 143, M/F, 20-54 yrs	Validated FFQ, 80 items Cancer registry, Death certificates	Total	975 vs. 581	0.82 (0.51, 1.34)	Age, energy intake, sex, BMI, height, smoking /NR
Studies that reported dietary calcium intake only (populations with a low (<5%) supplement use)								
Ishihara, 2008, Japan, [34]	JPHC Study	1995/99-2004, 7.8 yrs	74639, CRC:797, M/F, 45-74 yrs	Validated FFQ, 138 items Cancer registry, Death certificates	Dietary	754 vs. 318	0.79 (0.62, 1.02)	Age, energy intake, sex, study area, BMI, PA, smoking, alcohol, red meat, fruits, vegetables, folate, vitamin B-6, vitamin B-12, supplement use, endoscopy, menopausal status (women) /NR
Shin, 2006, China, [38]	Shanghai Women's Health Study	1997/2000-2004, 5.74 yrs	73215, CRC:220, F, 40-70 yrs	Validated FFQ, 77 items Cancer registry, Vital statistics registry	Dietary	672 vs. 243	0.60 (0.30, 1.00)	Age, energy intake, education, FH, PA, smoking, alcohol, vitamin supplements use, menopausal status /NR

Kesse, 2005, France, [37]	E3N-EPIC Study	1993/95-2000, 6.9 yrs	67484, CRC: 172, F, 40-65 yrs	Validated FFQ, 208 items, Medical records	Dietary	1321 vs. 668	0.72 (0.47, 1.10)	Age, energy intake, education, FH, BMI, PA, smoking, alcohol /calcium-vitamin D supplementation for osteoporosis treatment, red meat, processed meat, saturated fat fiber, folate
Jarvinen, 2001, Finland, [35]	Social Insurance Institution's Mobile Clinic Survey	1967/72-1991, 19.6 yrs	9959, CRC:72, M+F, ≥ 15 yrs	Non-validated FFQ, ≥100 items Cancer registry	Dietary	1860 vs. 864	1.43 (0.61, 3.39)	Age, energy intake, sex, occupation, geographical area, BMI, smoking /fiber, folate
Kampman, 1994, Netherland, [36]	Netherlands Cohort Study of diet and cancer	1986-1989, 3.3 yrs	3542, CRC:443, M+F, 55-69 yrs	Validated FFQ, 150 items Cancer registries, Pathology register	Dietary	1288 vs. 596	0.92 (0.64, 1.34)	Age, energy intake, sex, FH, BMI, fat, dietary fiber, history of gallbladder surgery /education, smoking, vitamin supplement use
Studies that reported dietary calcium intake only (populations with an appreciable supplement use)								
Key, 2011, UK, [41]	UK Dietary Cohort Consortium	(1985-2003)-(2003-2006), 4-16 yrs	2516, CRC:565, M+F, 61.7 yrs	Food diary Cancer registries, Office of National Statistics	Dietary	1089 vs. 582	1.22 (0.88, 1.69)	Age, calendar time, energy intake, sex, education, social class, height, weight, PA, smoking, alcohol, fiber /NR
Li, 2011, Germany, [42]	EPIC-Heidelberg	(1994-1998)-2010, 11 yrs	24323 CRC:201 M+F 35-64 yrs	Validated-FFQ, NR Medical records, Death certificates	Dietary	1131 vs. 512	0.80 (0.50, 1.30)	Age, energy intake, sex, education, BMI, waist-to-hip ratio, PA, smoking, alcohol, meat, fiber, vitamin D, vitamin K2, calcium/vitamin D supplements /NR
Terry, 2002, Sweden, [43]	Swedish Mammography Screening Cohort	1987/90-2000, 11.3 yrs	61463, CRC:572, F, 67 yrs	Validated FFQ, 67 items Medical records,	Dietary	914 vs. 486	0.72 (0.56, 0.93)	Age, energy intake, education, BMI, alcohol, red meat, saturated fat, folic acid, vitamin C, vitamin D /NR

				Cancer registries				
Pietinen, 1999, Finland, [40]	ATBC Cancer Prevention Study	1985/88-1995, 8 yrs	27111, CRC:185, M, 50-69 yrs	Validated FFQ, 276 items Cancer registry	Dietary	1789 vs. 856	0.60 (0.40, 0.90)	Age, energy intake, randomization assignment, education, BMI, occupational PA, smoking, alcohol /NR
Kato, 1997, USA, [20]	New York University Women's Health Study	1985/91-1994, 7.1 yrs	14727, CRC:100, F, 34-65	Validated FFQ, 70 items Medical records, Cancer registries	Dietary	1082 vs. 328	0.71 (0.39, 1.28)	Age, energy intake, place at enrollment, education /race, religion, BMI, height, aspirin use

*Two publications were combined to calculate estimates for CRC

Abbreviations: BMI=Body Mass Index; F=Females; FH=Family History; HRT=Hormone Replacement Therapy; M=Males; M/F=estimates were reported separately for males and females but combined using fixed-effects model; M+F=combined estimates for both sexes were reported in the original study; NR=Not Reported; NSAID=Non-Steroidal Anti-Inflammatory; PA=Physical Activity

Table 2. Summary results from subgroup analyses of linear dose-response relationship between total/supplementary calcium intake and CRC risk

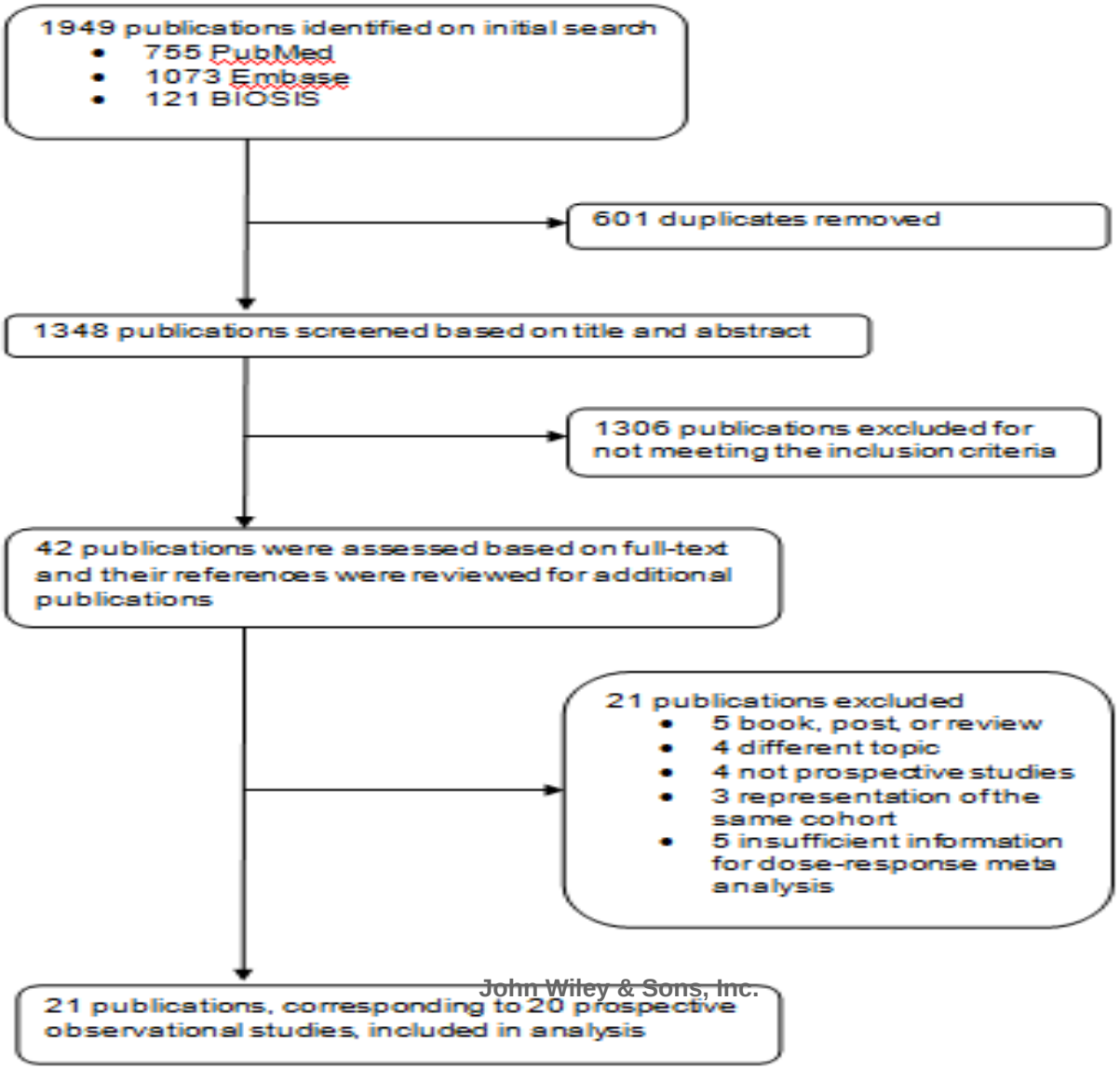
Subgroups		No. of studies	RR*(95% CI)	I^2(%)	$P_{heterogeneity}$ Within subgroup	$P_{heterogeneity}$ Between subgroups
All studies		15	0.92 (0.89, 0.95)	47	0.02	NA
1) by etiologic heterogeneity						
Subsite of CRC:						
CC		9	0.91 (0.87, 0.96)	21	0.26	0.76
RC	with the study by Jarvinen et al.	6	0.95 (0.83, 1.08)	59	0.03	
	without the study by Jarvinen et al.	5	0.90 (0.83, 0.97)	1	0.40	
2) by potential effect modifiers						
Sex:						
Men (total calcium intake)		7	0.92 (0.89, 0.95)	3	0.40	0.38
Women (total calcium intake)		11	0.93 (0.89, 0.96)	39	0.09	
Men (supplementary calcium intake)		3	0.84 (0.71, 1.00)	71	0.03	0.38
Women (supplementary calcium intake)		6	0.93 (0.88, 0.99)	49	0.08	
Geographical location:						
USA		8	0.93 (0.90, 0.96)	56	0.03	0.21
Asia		2	0.83 (0.72, 0.96)	0	0.33	
Europe	with the study by Jarvinen et al.	5	0.91 (0.83, 1.01)	33	0.20	
	without the study by Jarvinen et al.	4	0.88 (0.82, 0.96)	0	0.45	
Vitamin D fortification of dairy products:						
Yes		9	0.93 (0.90, 0.96)	57	0.02	0.69
No	with the study by Jarvinen et al.	6	0.90 (0.81, 1.00)	32	0.20	
	without the study by Jarvinen et al.	5	0.88 (0.81, 0.96)	0	0.41	
Mean calcium intake of the reference group:						
<700mg/d		12	0.93 (0.90, 0.96)	47	0.04	0.52
≥700mg/d	with the study by Jarvinen et al.	3	0.91 (0.79, 1.05)	53	0.12	
	without the study by Jarvinen et al.	2	0.85 (0.78, 0.94)	0	0.98	
3) by methodological characteristics						
No of cases:						
<400		7	0.92 (0.84, 1.01)	58	0.03	0.94

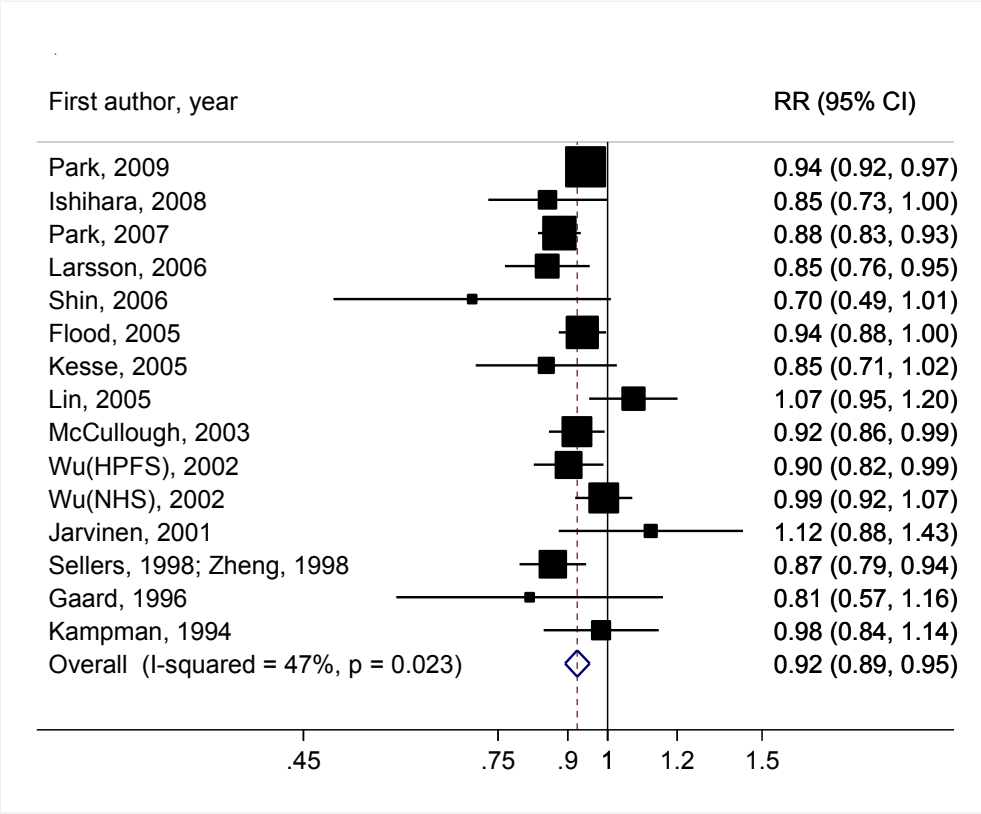
≥400	8	0.93 (0.90, 0.96)	40	0.11	
Duration of follow-up:					
<10 yrs	9	0.91 (0.88, 0.95)	36	0.13	0.25
≥10 yrs	6	0.96 (0.88, 1.04)	62	0.02	
Dietary questionnaire:					
Validated	14	0.92 (0.89, 0.95)	46	0.03	0.18
Not validated	1	1.12 (0.88, 1.43)	NA	NA	
Dietary assessment:					
At baseline	13	0.92 (0.89, 0.95)	49	0.02	0.51
Updated	2	0.95 (0.87, 1.04)	57	0.13	
Reverse causation:					
Addressed	9	0.93 (0.87, 0.99)	51	0.04	0.98
Not addressed	6	0.93 (0.89, 0.96)	44	0.11	
Adjustment for confounders:					
Smoking:					
Yes	14	0.93 (0.90, 0.96)	45	0.04	0.30
No	1	0.87 (0.79, 0.95)	NA	NA	
Alcohol:					
Yes	10	0.93 (0.90, 0.97)	43	0.07	0.11
No	5	0.90 (0.85, 0.96)	32	0.21	
Red meat:					
Yes	9	0.94 (0.91, 0.97)	39	0.11	0.08
No	6	0.90 (0.84, 0.96)	34	0.19	
Fiber:					
Yes	8	0.93 (0.89, 0.97)	31	0.18	0.63
No	7	0.91 (0.85, 0.97)	62	0.02	
Vitamin D:					
Yes	4	0.93 (0.88, 0.98)	44	0.15	0.88
No	11	0.92 (0.88, 0.96)	53	0.02	
Folate:					
Yes	7	0.94 (0.91, 0.97)	17	0.30	0.28
No	8	0.91 (0.86, 0.96)	52	0.04	
Physical activity:					
Yes	11	0.92 (0.89, 0.96)	51	0.03	0.94
No	4	0.93 (0.83, 1.05)	45	0.14	
Energy intake:					
Yes	15	0.92 (0.89, 0.95)	47	0.02	NA
No	0	NA	NA	NA	
Body mass index:					
Yes	13	0.93 (0.90, 0.96)	43	0.05	0.17

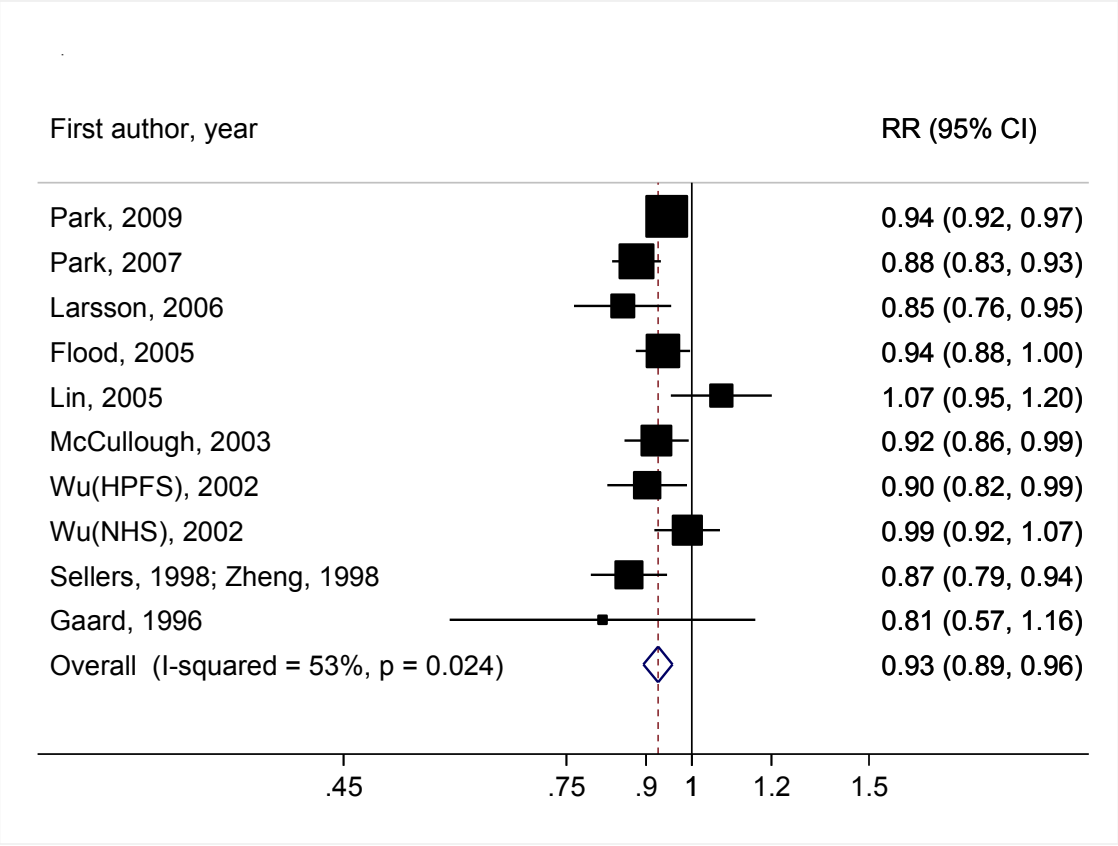
No	2	0.84 (0.73, 0.97)	19	0.27	
Multivitamin use:					
Yes	10	0.92 (0.88, 0.97)	52	0.03	0.82
No	5	0.93 (0.89, 0.97)	35	0.19	
Screening:					
Yes	4	0.94 (0.89, 0.98)	25	0.26	0.71
No	11	0.92 (0.88, 0.96)	55	0.01	
NSAID use:					
Yes	6	0.92 (0.88, 0.95)	38	0.15	0.67
No	9	0.93 (0.87, 0.99)	51	0.04	
Family history:					
Yes	11	0.92 (0.89, 0.96)	55	0.01	0.91
No	4	0.93 (0.85, 1.01)	25	0.26	
Prior adenoma:					
Yes	2	0.96 (0.80, 1.17)	89	0.003	0.63
No	13	0.92 (0.90, 0.95)	29	0.15	

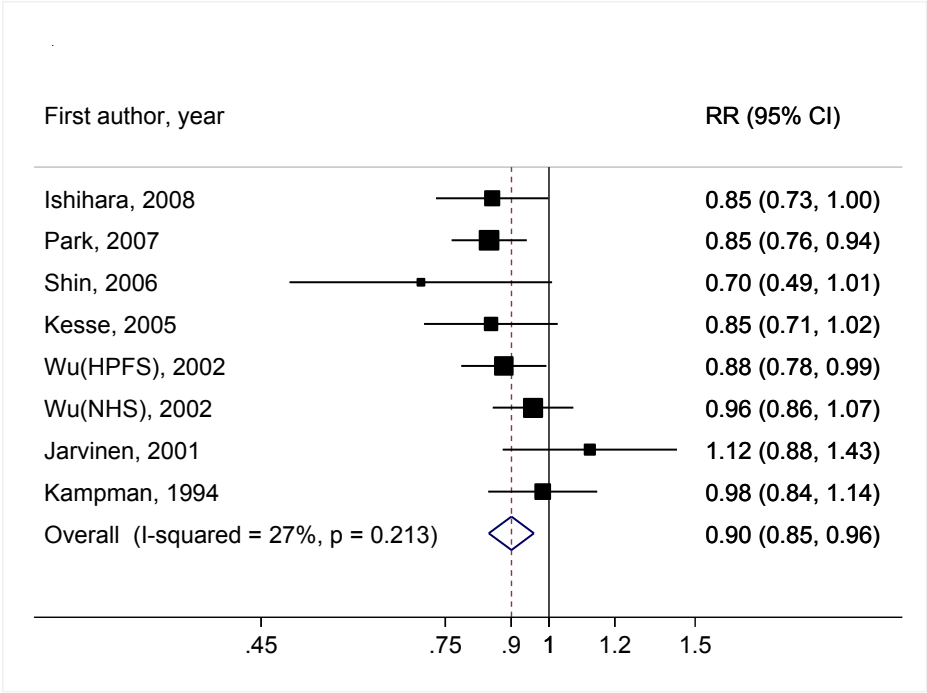
*RR for a 300mg/day increase in calcium intake

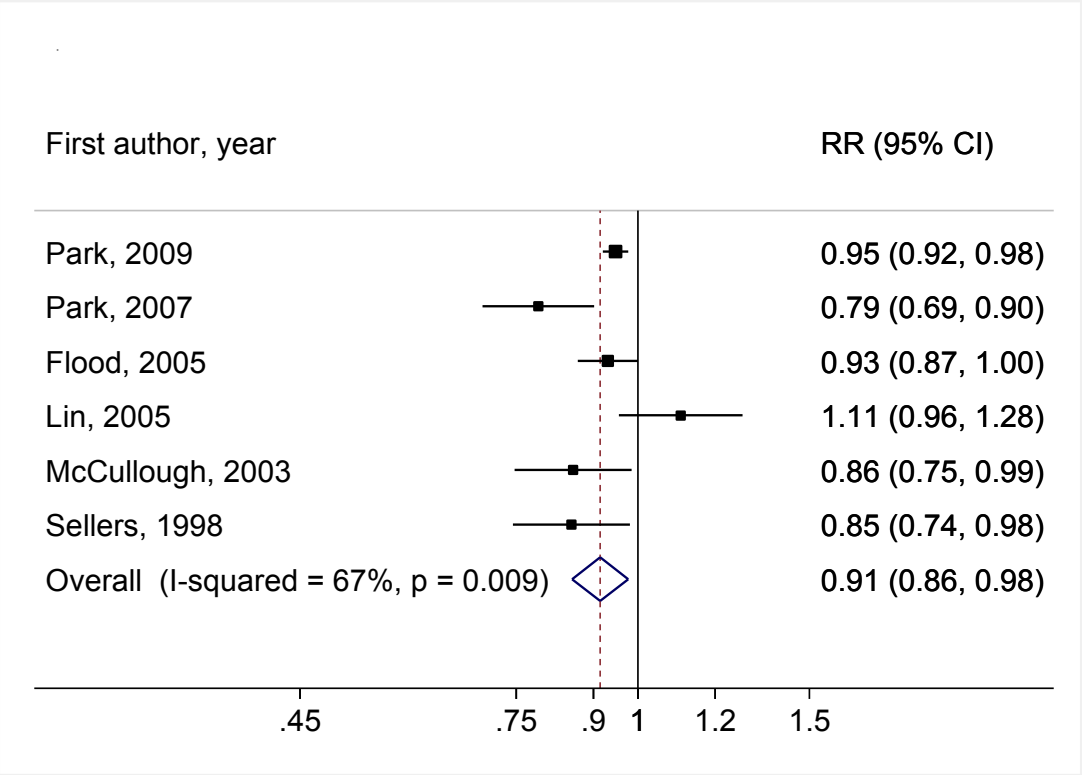
Abbreviations: NA=Not Applicable; NSAID=Non-Steroidal Anti-Inflammatory Drug

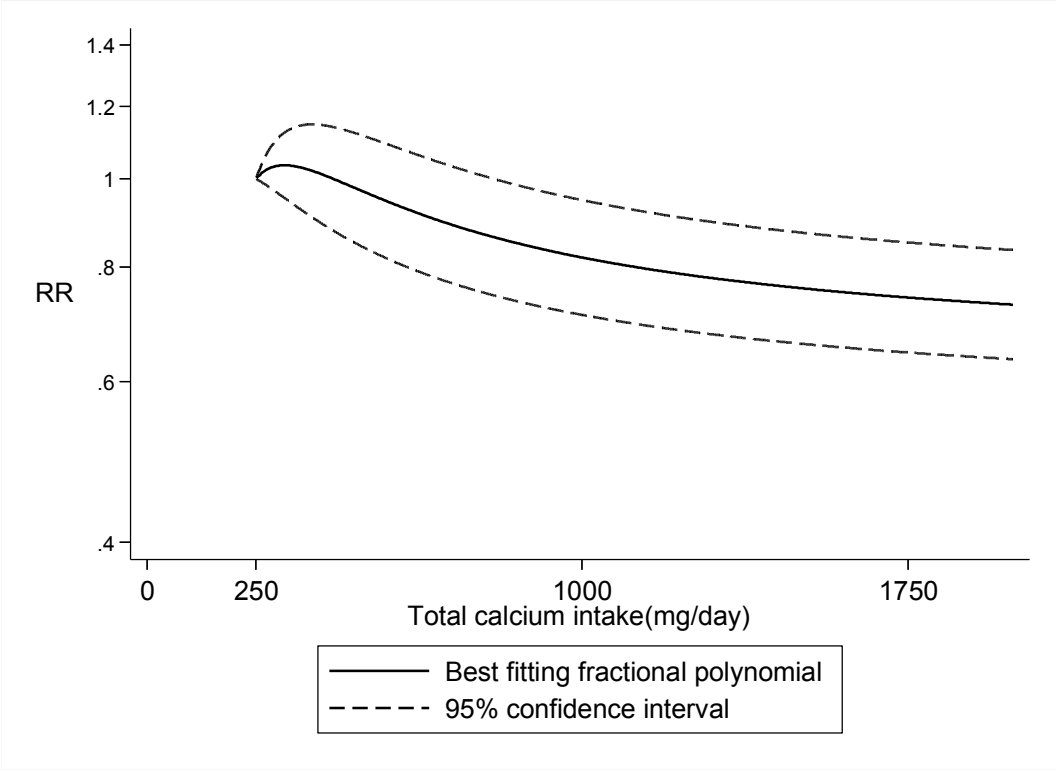



First author, year
RR (95% CI)
Park, 2009
0.94 (0.92, 0.97)
Ishihara, 2008
0.85 (0.73, 1.00)
Park, 2007
0.88 (0.83, 0.93)
Larsson, 2006
0.85 (0.76, 0.95)
Shin, 2006
0.70 (0.49, 1.01)
Flood, 2005
0.94 (0.88, 1.00)
Kesse, 2005
0.85 (0.71, 1.02)
Lin, 2005
1.07 (0.95, 1.20)
McCullough, 2003
0.92 (0.86, 0.99)
Wu(HPFS), 2002
0.90 (0.82, 0.99)
Wu(NHS), 2002
0.99 (0.92, 1.07)
Jarvinen, 2001
1.12 (0.88, 1.43)
Sellers, 1998; Zheng, 1998
0.87 (0.79, 0.94)
Gaard, 1996
0.81 (0.57, 1.16)
Kampman, 1994
0.98 (0.84, 1.14)
Overall (I-squared = 47%, p = 0.023)
0.92 (0.89, 0.95)
.45
.75
.9
1
1.2
1.5


First author, year
RR (95% CI)
Park, 2009
0.94 (0.92, 0.97)
Park, 2007
0.88 (0.83, 0.93)
Larsson, 2006
0.85 (0.76, 0.95)
Flood, 2005
0.94 (0.88, 1.00)
Lin, 2005
1.07 (0.95, 1.20)
McCullough, 2003
0.92 (0.86, 0.99)
Wu(HPFS), 2002
0.90 (0.82, 0.99)
Wu(NHS), 2002
0.99 (0.92, 1.07)
Sellers, 1998; Zheng, 1998
0.87 (0.79, 0.94)
Gaard, 1996
0.81 (0.57, 1.16)
Overall (I-squared = 53%, p = 0.024)
0.93 (0.89, 0.96)
.45
.75
.9
1
1.2
1.5


First author, year
RR (95% CI)
Ishihara, 2008
0.85 (0.73, 1.00)
Park, 2007
0.85 (0.76, 0.94)
Shin, 2006
0.70 (0.49, 1.01)
Kesse, 2005
0.85 (0.71, 1.02)
Wu(HPFS), 2002
0.88 (0.78, 0.99)
Wu(NHS), 2002
0.96 (0.86, 1.07)
Jarvinen, 2001
1.12 (0.88, 1.43)
Kampman, 1994
0.98 (0.84, 1.14)
Overall (I-squared = 27%, p = 0.213)
0.90 (0.85, 0.96)
.45
.75
.9
1
1.2
1.5


First author, year
RR (95% CI)
Park, 2009
0.95 (0.92, 0.98)
Park, 2007
0.79 (0.69, 0.90)
Flood, 2005
0.93 (0.87, 1.00)
Lin, 2005
1.11 (0.96, 1.28)
McCullough, 2003
0.86 (0.75, 0.99)
Sellers, 1998
0.85 (0.74, 0.98)
Overall (I-squared = 67%, p = 0.009)
0.91 (0.86, 0.98)
.45
.75
.9
1
1.2
1.5


1.4
1.2
1
.8
.6
.4
RR
0
250
1000
1750
Total calcium intake(mg/day)
Best fitting fractional polynomial
95% confidence interval

Online supplementary method

PubMed search:
("Colorectal Neoplasms"[Mesh] OR colorectal cancer*[tiab] OR colo rectal cancer*[tiab] OR colorectal neoplas*[tiab] OR colorectoral malignanc*[tiab] OR colorectal tumor*[tiab] OR colorectal tumour*[tiab] OR colorectal carcinoma*[tiab] OR colo rectal carcinoma*[tiab] OR colorectal adenoma*[tiab] OR cancer of the colon[tiab] OR cancer of the rectum[tiab] OR rectal cancer*[tiab] OR rectal neoplas*[tiab] OR rectal tumor*[tiab] OR rectal tumour*[tiab] OR rectal adenoma*[tiab] OR rectal carcinoma*[tiab] OR colon cancer*[tiab] OR colon neoplas*[tiab] OR colonic neoplas*[tiab] OR colon tumor*[tiab] OR colonic tumor*[tiab] OR colon tumour*[tiab] OR colonic tumour*[tiab] OR colon adenoma*[tiab] OR colonic adenoma*[tiab] OR colonic cancer*[tiab] OR colon carcinoma*[tiab] OR colonic carcinoma*[tiab]) AND ("Calcium, Dietary"[Mesh] OR (calcium[tiab] AND (intake[tiab] OR dietary[tiab] OR diet[tiab] OR supplementation[tiab] OR supplements[tiab] OR supplement[tiab] OR food[tiab] OR foods[tiab])))

Embase search:
('calcium intake'/de OR (calcium:ab,ti AND (intake:ab,ti OR diet*:ab,ti OR supplement*:ab,ti OR food*:ab,ti))) AND ('colon cancer'/exp OR 'rectum tumor'/exp OR (colon OR colonic OR colorectal OR 'colo rectal' OR rectal OR rectum) NEAR/3 (cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR carcinom* OR adenoma*))

BIOSIS search:
(calcium AND (intake OR diet* OR supplement* OR food*)) AND (colorectal cancer* OR colo rectal cancer* OR colorectal neoplas* OR colorectoral malignanc* OR colorectal tumor* OR colorectal tumour* OR colorectal carcinoma* OR colo rectal carcinoma* OR colorectal adenoma* OR cancer of the colon OR cancer of the rectum OR rectal cancer* OR rectal neoplas* OR rectal tumor* OR rectal tumour* OR rectal adenoma* OR rectal carcinoma* OR colon cancer* OR colon neoplas* OR colonic neoplas* OR colon tumor* OR colonic tumor* OR colon tumour* OR colonic tumour* OR colon adenoma* OR colonic adenoma* OR colonic cancer* OR colon carcinoma* OR colonic carcinoma*)i