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Calcium supplementation in colorectal cancer prevention: A systematic meta-analysis of adverse events

Xue Mei LUO[1]; Shahanavaj KHAN[2,3,4,*]; Abdul MALIK[2]; Fahad M. ALDAKHEEL[5]; Anis Ahmad CHAUDHARY[6]; Shouki BAZARBASHI[7]; Fatemeh TABATABAIE[8]

[1] Department of General Surgery, Mianzhu People's Hospital of Sichuan, Mianzhu, China
[2] Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[3] Department of Biosciences, Shri Ram Group of College (SRGC), Muzaffarnagar, India
[4] Department of Health Sciences, Novel Global Community Educational Foundation, Sydney, Australia
[5] Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia
[6] Department of Biology, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSUI), Riyadh, Saudi Arabia
[7] Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[8] Shiraz University of Medical Sciences, Shiraz, Iran

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Abstract: Despite the multiple systematic reviews and meta-analyses accumulating evidence on the preventive effect of calcium supplementation for colorectal cancer, most of the associated adverse effects are not systematically analyzed. The aim of the study is evaluating adverse events associated with calcium supplementation for colorectal cancer prevention through a systematic meta-analysis. We searched Medline, PubMed Central, EMBASE (Excerpta Medica database), Scopus, Cochrane Central Register of Controlled Trials, and Web of Science published in English from database inception up to 31 July 2019. In the current systematic meta-analysis, we included human studies (including cohort studies, clinical trials, case-control studies) on supplementation of calcium in patients with or at risk of colorectal cancer. Assessment of the quality of included studies was performed by Jadad score. Information on the patient population, number of enrolled subjects in each group, dose of calcium supplementation, duration of calcium supplementation, and reported adverse events were gathered. The data were pooled for incidence rates for any adverse event during the study period regardless of causality association. We identified 6 studies, comprising 4583 participants that met the inclusion criteria. Meta-analysis on pooled incidence rates for adverse event during study period showed no statistically significant increased risk for cancer (OR = 0.92, 95% CI: 0.70–1.21, P = 0.577; I^2 = 0.0%, P = 0.731), coronary revascularization (OR = 1.12, 95% CI: 0.79–1.59, P = 0.492; I^2 = 0.0%, P = 0.957), myocardial infarction (OR = 0.81, 95% CI: 0.34–1.91, P = 0.634; I^2 = 67.9%, P = 0.047), stroke (OR = 0.75, 95% CI: 0.42–1.33, P = 0.332, I^2 = 0.00%, P = 0.717), Transient Ischemic Attack (TIA) (OR = 1.37, 95% CI: 0.28–6.51, P = 0.692, I^2 = 81.9%, P = 0.002), urolithiasis (OR = 1.23, 95% CI: 0.75–2.01, P = 0.410; I^2 = 0.0%, P = 0.851), fracture (OR = 0.98, 95% CI: 0.70–1.37, P = 0.938; I^2 = 37.8%, P = 0.152) and death (OR = 1.05, 95% CI: 0.71–1.56, P = 0.786, I^2 = 12.2%, P = 0.317) in patients receiving calcium supplementation for colorectal cancer prevention compared to control. Based on the results of Egger test, publication bias was not observed among the studies (P = 0.262). The current result of the meta-analysis on human studies reporting adverse events associated with calcium supplementation for the prevention of colorectal cancer demonstrated no statistically significant increased risk for the development of adverse events compared to control groups.

List of Abbreviations

EMBASE: Excerpta Medica database
PICOS: population, intervention, control, outcome, study
CaSR: calcium-sensing receptors
PRISMA: preferred reporting items for systematic reviews and meta-analyses
RCTs: randomized controlled trials
RevMan: review manager

*Address correspondence to: Shahanavaj Khan, sdkhan@ksu.edu.sa
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Introduction

Colorectal cancer incidence varies markedly worldwide. Globally, it is the third most common detected cancer in males and the second in females (Favoriti *et al*., 2016). In 2018, 1.8 million new patients and 861,000 deaths from colorectal cancer is reported worldwide (Macrae, 2016). Lifestyle and infections are considered more important factors in development of colorectal cancers (Chapkin *et al*., 2020). Obesity, lack of physical activity, smoking, and alcohol are known risk factors for colorectal cancer (Abdifard *et al*., 2016). Minority of cases are associated with a specific genetic susceptibility such as familial adenomatous polyposis and hereditary non-polyposis colon cancer. Most of cases begin as benign lesions like polyp undergoing malignant transformation through the time (Rodrigues *et al*., 2020).

Different interventions are suggested for modifying the colorectal cancer risk (Janne and Mayer, 2000). Dietary supplements, physical activity, non-steroidal anti-inflammatory drugs, aspirin, and hormones are among the preventive measures with the most supporting evidence (Afrin *et al*., 2018; Barry *et al*., 2018; Shaw *et al*., 2018; Wilkins *et al*., 2018). Fibers, folic acid, pyridoxine, garlic, fish oil, vitamin D, and calcium are the most studied supplements for colorectal cancer prevention (Murphy *et al*., 2019; Waluga *et al*., 2018).

Calcium is an essential molecule to maintain human body health. Calcium is needed for different physiologic functions in human body including skeletal, neurologic, cardiologic, and muscular system functions (Pravina *et al*., 2013). The most popular function of calcium is in maintaining skeletal system (Power *et al*., 1999). Hypocalcemia may lead to osteoporosis or osteomalacia. Increased contractility of the muscles is caused by the raised extracellular ionized Calcium. This effect is not limited to skeletal muscles and is also present in cardiac muscle. Thus, problems in calcium hemostasis may lead to weakness, muscle spasm and heart failure or arrhythmia. Calcium also affects nervous system excitability. Calcium affects cellular permeability which cause its important role in allergic conditions (Pu *et al*., 2016).

Calcium supplementation is largely studied for its effect on colorectal cancer risk reduction in patients at risk, with promising results. These studies vary on the level of evidence and include case controls, cohorts, and clinical trials (Flood *et al*., 2005; Grau *et al*., 2003; Jenab *et al*., 2010). A systematic review and meta-analysis of 3 studies on the role of calcium supplementation for 3–4 years in preventing recurrence of colorectal adenomas in 1,279 patients found a significantly lower recurrence rate in patients receiving calcium supplementation compared to placebo (RR: 0.80, CI: 0.68, 0.93; $P = 0.004$) (Shaukat *et al*., 2005). Another recent systematic review and meta-analysis of 5 trials assessing the preventive effect of calcium supplementation in patients at risk of colorectal cancer including 2234 patients revealed the positive effect of calcium supplementation (RR: 0.88) (Veettil *et al*., 2017). This study also demonstrated the superior effect of elemental calcium dose of more than 1600 mg/day (RR, 0.74) compared to less than 1200 mg/day (RR, 0.84). Multiple biologically probable mechanisms are supposed for the protective effect of calcium supplementation in colorectal cancer. Calcium ameliorates inflammation and bile acid irritation on the colon wall. Moreover, intracellular calcium suppresses neoplastic promoting pathways in colon epithelial cells. It is also suggested that calcium can repress bile acid toxicity in the colon (Han *et al*., 2015).

Despite the beneficial preventive effects of calcium supplementation on colorectal cancer, some studies suggested health risks and adverse events associated with calcium supplementation. In a randomized controlled trial on 1471 postmenopausal women receiving calcium supplementation, the adjusted rate of myocardial infarction in the calcium group was significantly higher than the rate in the placebo group (RR: 2.12, 95% CI: 1.01–4.47) (Bolland *et al*., 2008). The result of a prospective cohort study on 91,731 women suggested an increased risk of kidney stones in patients receiving non-dietary calcium supplementation (RR: 1.20, 95% CI: 1.02–1.41) (Curhan *et al*., 1997). Additionally, other potential adverse effects of calcium supplementation such as constipation, metabolic syndrome, and age-related macular degeneration were reported (Kakigi *et al*., 2015; Noe *et al*., 2015; Prince *et al*., 2006).

Despite the multiple systematic reviews and meta-analyses accumulating evidence on the preventive effect of supplementation of calcium on the risk of colorectal cancer, the associated adverse events were not systematically reviewed. The aim of this study to evaluates the adverse events associated with calcium supplementation for colorectal cancer prevention in a systematic meta-analysis.

Materials and Methods

Database search strategy

A comprehensive search was performed to retrieve any reported adverse event associated with calcium supplementation in patients with or at risk of colorectal cancer from published literature. The following databases were searched since initiation up to 31 July 2019; Medline, PubMed Central, EMBASE (Excerpta Medica database), Scopus, Cochrane Central Register of Controlled Trials, and Web of Science. Keywords including “trial”, “cohort”, “case-control”, “observational”, “interventional”, “patients” were added to “colorectal”, “colon” plus “calcium” and were used for database search. Our search was limited to studies reported in the English language.

Selection criteria

To meet the study objectives, human studies (including cohort studies, clinical trials, and case-control studies) on supplementation of calcium in patients with or at risk of colorectal cancer were included. To be included in the meta-analysis, studies should include information on the observed adverse events in two study groups (the active group receiving calcium supplementation and the control group not receiving calcium supplementation) (Table 1).

The following studies were excluded: (1) non-original reports; (2) experimental models and *in-vitro* studies; (3) reports not mentioning any information about adverse

TABLE 1

PICOS (Population, intervention, control, outcome, study) criteria for the systematic review

Participants	Patients with or at risk of colorectal cancer
Interventions	Calcium supplementation
Comparisons	Not receiving calcium supplementation
Outcomes	Any reported adverse event
Study design	A systematic review of human studies

events; (4) studies on the concomitant use of calcium with other supplementation in all patients; (5) studies on only dietary calcium intake without calcium supplementation; and (6) studies in which full text could not be sourced.

Data extraction

Bibliographic information of all manuscripts retrieved through database search was transferred to Endnotes V.X6. Data extraction was performed by two independent reviewers. Disagreements were resolved by a third reviewer.

Data were documented in predefined forms. Information on the patient population, numbers in each study group, dose of calcium supplementation, duration of calcium supplementation, reported adverse events in each group were extracted from each included study. The data were pooled for incidence rates for any adverse event during the study period regardless of causality association.

Study quality and risk of bias

Assessment of the quality of included studies was performed by Jadad score.

Statistical analysis

A comparison of reported adverse events was made between interventions by collecting data from studies by direct meta-analysis technique. Meta-analysis of the available data was performed using Review Manager (RevMan V.5.1) software. Dichotomous outcomes were summarized as risk (relative) ratios.

Results

Description of search

After retrieving data from various international databases, 210 articles were retrieved. Omitting duplicate articles, 162 articles were remained which sent for evaluation of the topics and abstracts. Passing this stage, 69 articles entered the full texts review and finally, 6 eligible articles entered the final analysis. It should be noted that the references of the included articles were also reviewed to add relevant studies. The flowchart of the included studies is displayed in Fig. 1.

Characteristics of the included studies

The characteristics of the studies included in the meta-analysis are presented in Table 2. According to the geographical area, four studies were performed on the North American population and two on the French and Dutch population.

Meta-analysis and data synthesis

Cancer

Among the included studies, three randomized controlled trials (RCTs) assessed the risk of development of cancer in patients receiving calcium supplementation. Meta-analysis revealed less incidence of cancer in intervention group compared to placebo group, but these findings were not statistically significant (OR = 0.92, 95% CI: 0.70–1.21, $P = 0.577$; $I^2 = 0.0\%$, $P = 0.731$).

Coronary revascularization

Three studies reported risk of coronary revascularization. No overall significant effect was observed in the intervention compared to control group (OR = 1.12, 95% CI: 0.79–1.59. $P = 0.492$; $I^2 = 0.0\%$, $P = 0.957$).

Myocardial infarction

Among the included studies, two RCTs assessed the risk of myocardial infarction. Meta-analysis revealed lower incidence of myocardial infarction in patients receiving calcium supplementation compared to control, but these findings were not statistically significant (OR = 0.81, 95% CI: 0.34–1.91, $P = 0.634$; $I^2 = 67.9\%$, $P = 0.047$).

Stroke

Three studies assessed the risk of stroke in studied patients. Pooled effect of intervention compared to control showed not significant association (OR = 0.75, 95% CI: 0.42–1.33, $P = 0.332$, $I^2 = 0.00\%$, $P = 0.717$).

Transient Ischemic Attack (TIA)

Two studies assessed the effect of calcium supplementation on the risk of TIA. Despite the increased risk, the statistical analysis indicated no significant effect of calcium supplement compared to control (OR = 1.37, 95% CI: 0.28–6.51, $P = 0.692$; $I^2 = 81.9\%$, $P = 0.002$).

Urolithiasis

Two studies reported this adverse event in patients who received calcium supplementation. No overall significant effect was observed in the intervention compared to control group (OR = 1.23, 95% CI: 0.75–2.01, $P = 0.410$; $I^2 = 0.0\%$, $P = 0.851$).

Fracture

Two studies assessed the effect of calcium supplementation on the risk of fractures. The results indicated no significant effect of calcium supplementation compared to control (OR = 0.98, 95% CI: 0.70–1.37, $P = 0.938$, $I^2 = 37.8\%$, $P = 0.152$).

Death

Three studies assessed the risk of death in the patient population. Pooled effect of intervention compared to control showed no significant association (OR = 1.05, 95% CI: 0.71–1.56, $P = 0.786$; $I^2 = 12.2\%$, $P = 0.317$).

Publication bias

Based on the results of the Egger test, publication bias was not observed among the included studies ($P = 0.262$). Fig. 2 shows the funnel plot for each adverse event included in the meta-analysis of these studies.

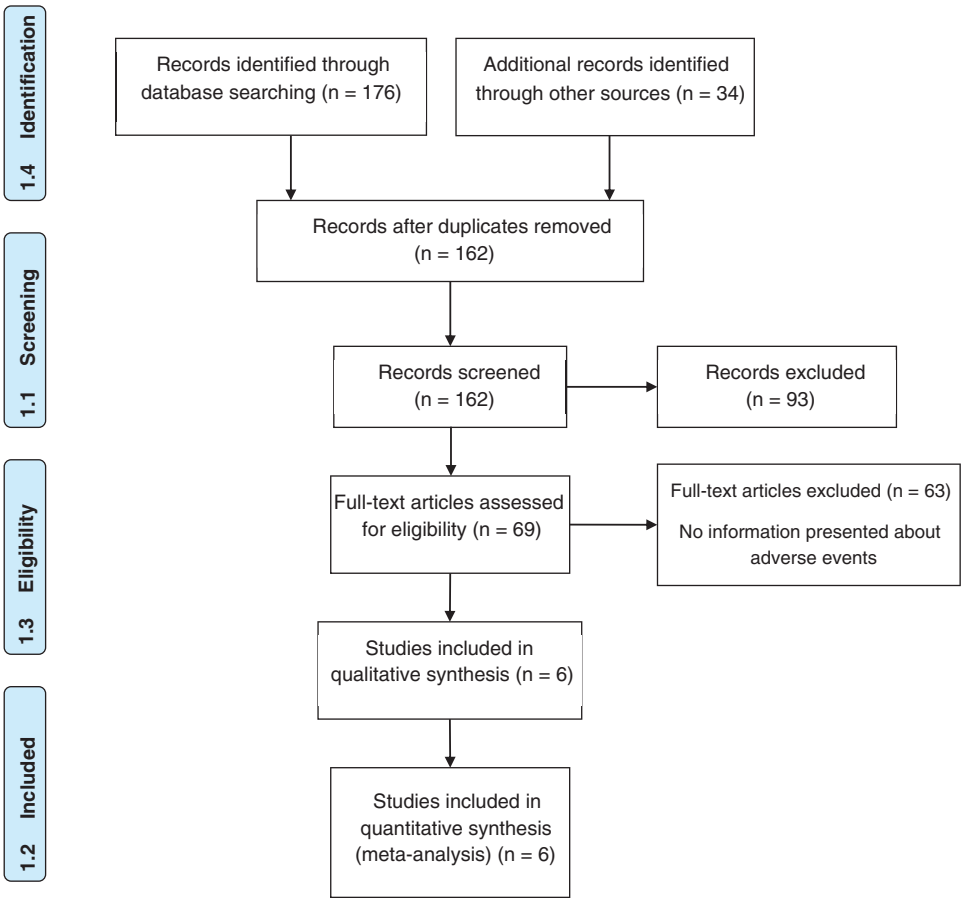

FIGURE 1. PRISMA flow diagram for included studies.

Discussion

Calcium homeostasis play important roles in different systems of our body, including skeletal, hormonal, cardiovascular, neurologic, and gastrointestinal systems (Peacock, 2010). Dietary calcium is absorbed throughout the small intestine. Absorbed calcium is mostly deposited into bones with excessive amounts excreted in the urine and feces. The main pathways in the homeostasis of calcium are regulated by parathyroid hormone and calcitonin (Veldurthy *et al.*, 2016).

The preventive effect of calcium in colorectal cancer is considered to be through extracellular calcium-sensing receptors (CaSR) in the colon. The CaSR is involved in cell proliferation and differentiation. Accumulating evidence suggests that the CaSR might play a protective role against colorectal cancer. CaSR expression was shown to be reduced in colorectal cancer (Iamartino *et al.*, 2018).

Different mechanisms are proposed for the potential adverse effects of calcium supplementation. Transiently elevated calcium levels by calcium supplements may contribute to cardiovascular risk. This risk is considered to be associated with calcium-sensing receptors on platelets that are activated with elevated serum calcium and cause increased blood coagulability. (Chin *et al.*, 2017) It is also supposed that calcium supplementation may increase the urinary calcium excretion which can lead to stone formation or progression through hypercalciuria. However, this effect is not observed in patients receiving dietary calcium (Sorensen, 2014).

Notwithstanding the proposed mechanisms for adverse events associated with calcium supplementation, our results demonstrated no significant increase in the mentioned side effects in patients receiving calcium supplementation for colorectal cancer prevention compared to control groups.

The main strength of this study was its novelty. Despite the popular use of calcium supplementation in patients at the risk of colorectal cancer, no research has previously accumulated the evidence for potential risks of this intervention. This study has evaluated the risk of calcium supplementation in this population of patients for the first time. The use of the meta-analysis method was another important point of study which let us accumulate the observed adverse events in 2300 patients of 6 different human studies and compare it with 2283 controls. The use of control patients for statistical comparison made it possible to evaluate the potential causality of observed adverse events to calcium supplementation. The use of control comparison in the evaluation of adverse effects is of special importance in high-risk patient populations like patients with colorectal cancer which different adverse events may be observed in them without a causal relationship with the specific intervention.

There are some limitations to this systematic study. The majority of studies on calcium supplementation in colorectal cancer did not report information on adverse events. Studies included in this review were not similar in follow-up duration and the dose of calcium supplementation. The

TABLE 2

Characteristics of studies included in systematic review and meta-analysis

Trial	Dose (mg elemental Ca/day)	Treatment duration	Number in the calcium group	Number in the control group	Reported adverse events			Randomization	Randomization method	Blinding	Blinding method	Excluded described
(Calderwood *et al.*, 2019)	1200	55 ± 15 months	760	745		Calcium	Control	Observational				
					Death	15	16					
					Myocardial Infarction	9	6					
					Coronary revascularization	12	12					
					Stroke	7	13					
					Transient ischemic attack	5	1					
					Cancer	45	46					
					Urolithiasis	16	14					
					Fracture	37	31					
(Baron *et al.*, 2015)	1200	3–5 years	840	835		Calcium	Control	Yes	Yes	Yes	No	No
					Death	13	12					
					Myocardial Infarction	2	9					
					Coronary revascularization	12	8					
					Stroke	3	5					
					Transient ischemic attack	0	3					
					Cancer	46	46					
					Urolithiasis	20	15					
					Fracture	37	43					
					Hypercreatininemia	58	40					
					Hypercalcemia	17	5					
(Baron *et al.*, 1999)	1200	4 years	464	466		Calcium	Control	Yes	Yes	Yes	Yes	Yes
					Death	25	22					
					Hospitalization	172	164					
					Cardiac disease	50	46					
					Stroke	12	11					
					Gastrointestinal disease	38	32					
					Cancer	15	21					
					Stop treatment due to perceived toxicity	12	13					
(Bonithon-Kopp *et al.*, 2000)	2000	3 years	176	178	All adverse events (not specified)	26	12	Yes	Yes	No	No	Yes
(Cats *et al.*, 1995)	600	12 weeks	14	13	No adverse event observed			Yes	No	Yes	No	No
(Tu *et al.*, 2015)	2000	6 months	46	46	No adverse event observed			Yes	Yes	Yes	Yes	Yes

interaction between calcium and other supplementation used in colorectal cancer prevention like vitamin D, folic acid, pyridoxine, garlic, and fish oil was not evaluated in this study. Publication bias is another source of bias in the meta-analysis. Studies with a higher rate of adverse events are more prone not to be published in the literature. Language limitation of included studies is another potential source of bias in this systematic review.

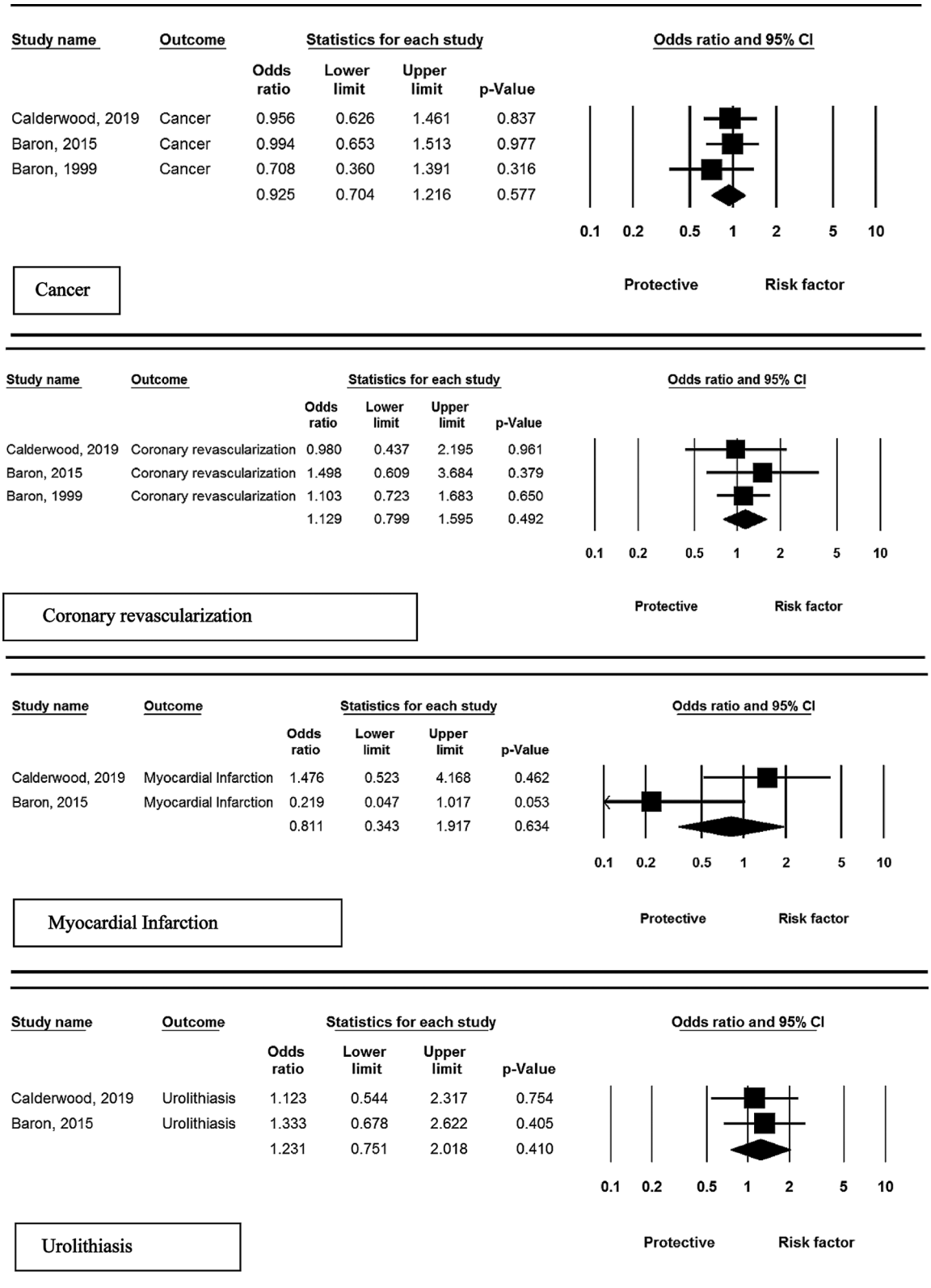

FIGURE 2. (continued)

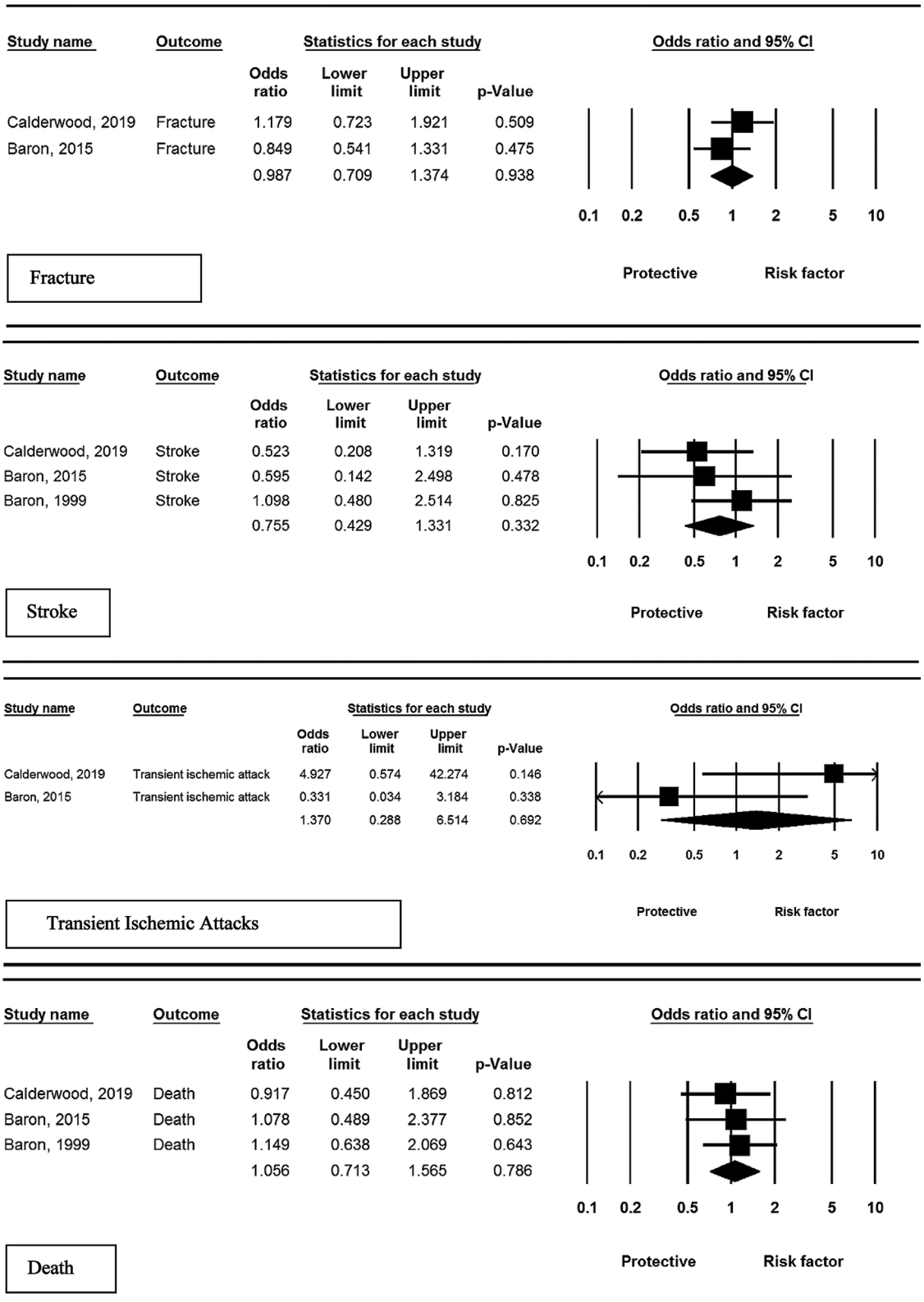

FIGURE 2. Results of meta-analysis, any adverse events: calcium *vs.* placebo.

Conclusion

A meta-analysis of human studies reporting adverse events associated with calcium supplementation for the prevention of colorectal cancer demonstrated no statistically significant increased risk for the development of adverse events compared to control groups.

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Availability of Data and Materials: All data generated or analyzed during this study are included in this published article.

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