REVIEW

Effect of drinking water calcium, magnesium, and hardness on colorectal cancer mortality: A systematic review

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ABSTRACT

Background and aim: This systematic review aimed to summarise findings from studies investigating the association between calcium, magnesium, and drinking water hardness and colorectal cancer mortality.
Methods: A systematic literature search was conducted on PubMed, Scopus, and Web of Science databases. The work was carried out according to the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was registered in Open Science Framework (OSF) Registries (https://doi.org/10.17605/OSF.IO/5HEVS).
Results: One hundred thirty-three records were identified, and at the end of the selection process, nine studies met the inclusion criteria. All the studies were conducted before 2011 in the same geographical area (Taiwan, China). All the studies suggested a protective effect of higher calcium concentration in drinking water towards colon cancer mortality, whereas the effects on rectal cancer mortality were mixed. High water hardness seems to be protective towards mortality from both cancer types.
Conclusions: This systematic review found interesting results on the potential role of calcium-rich water in the management of colon cancer. These results, however, should be confirmed in novel, large and preferably longitudinal studies conducted in other parts of the world before drawing definitive conclusions. (www.actabiomedica.it)

Key words: calcium, magnesium, hardness, drinking water, colorectal cancer

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Introduction

Colorectal cancer (CRC) is a malignant disease that causes premature death and represents a burden to the world population (1). In 2019, CRC was the third leading cause of cancer deaths (1.09 million), with 2.17 million incident cases, and an age-standardised mortality rate of 13.7 per 100 000 (1). Taken separately, colon cancer accounted for over 1.1 million new cases and over 0.5 million deaths in 2022 worldwide, whereas rectal cancer new cases and deaths were over 0.7 million and over 0.3 million, respectively (2,3). Moreover, CRC is the second leading cause of disability-adjusted life years (DALYs) for cancer worldwide (4). It also represents a disease associated with a high rate of morbidity and loss of healthy life years (5). Even though CRC is a leading cause of cancer mortality, it is a curable disease if diagnosed early (6). An individual's risk of developing CRC depends on many factors, including non-modifiable (e.g., increasing age, family history of CRC or colorectal polyps, familial adenomatous polyposis, Lynch syndrome, and inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis) (7) and lifestyle-related modifiable risk factors. According to the World Cancer Research Fund (WCRF) International, there is strong evidence that consuming red and/or processed meat, alcoholic drinks, being overweight or obese, and smoking increase the risk of CRC (8). Moreover, WCRF stated that being physically active decreases the risk of colon cancer, and consuming whole grains, other foods containing dietary fibre, dairy products and taking calcium supplements decrease CRC risk (8). Calcium is the most abundant mineral in the body, with almost all of it stored in bones and teeth, giving them structure and hardness. Its concentration is crucial for the subsistence of many physiological processes, such as hormone release (calcitonin and parathyroid), vascular function, muscular contractions and nerve message transmission. The D vitamin group of fat-soluble hormones is involved in the body's calcium absorption (9). The daily recommended intake of calcium is approximately 200 mg for infants (from birth to six months), 1300 mg for teenagers (from nine to 18 years) and 1000 mg for adults (from 19 to 70 years) (9). A relevant pair of evidence suggests that consumption of milk-based (dairy) products was associated with lower CRC incidence and mortality (10). Due to the high calcium content in milk, this could represent one of the major nutrients mediating the beneficial effect on CRC. However, dairy intake was also associated with increased prostate cancer risk (11), raising doubts about the massive intake of dairy products as 'healthy' sources of calcium. Calcium is also present in drinking water. Indeed, despite hydration as its main function, water constitutes a relevant source of minerals, detectable as macro-elements, required in daily 'mg' amounts (e.g., Ca, P, Na, K, Mg, Cl, S), and micro-elements, needed in daily 'μg' amounts (e.g., Fe, Cu, Zn, Mn, Se, I, Mo, Co). The contribution of drinking water minerals to total daily intake is often around 10%, although it may vary with water intake and water's chemical composition (12). Nevertheless, even contributions lower than 10% may benefit health status, especially if mineral intake from food is insufficient or the organism manifests some deficiency. A protective effect of calcium intake on colon cancer development has been proposed based on some evidence (13,14); the mechanism underlying this effect has been further elucidated, highlighting calcium's ability to bind free fatty acids and unconjugated bile acids, thereby lowering their toxic effects on the colorectum. In addition, *in vitro* studies suggested that it might also reduce cancer cell proliferation and promote cell differentiation, probably by influencing different cell-signalling pathways (15). However, detailed mechanisms remain unclear. Along with calcium, magnesium also represents a key element for human health. Almost all total body magnesium (≈ 99%) is in bone, muscles and non-muscular soft tissue and acts as a cofactor in more than 300 enzymatic reactions. Many pivotal physiologic reactions, such as metabolism, muscle contraction-relaxation, normal neurological function, and neurotransmitter release, are magnesium-dependent (16). Moreover, magnesium modulates cell proliferation and insulin signal transduction, is crucial for cell adhesion and the transmembrane transport of potassium and calcium ions, and is essential for maintaining the conformation of nucleic acids and for the structural function of proteins and mitochondria. There is also evidence of competition between magnesium and calcium for the same binding sites on plasma protein molecules (16).

A meta-analysis of cohort studies (17) indicated that high intakes of dietary calcium and magnesium were negatively associated with CRC risk, and a meta-analysis of case-control studies (17) indicated that high intakes of dietary calcium, magnesium, and potassium were negatively related to CRC occurrence. In addition, a meta-analysis of prospective cohort studies (18) found a statistically significant, nonlinear inverse association between dietary magnesium intake and CRC risk, with the most significant reduction observed at 200–270 mg/day. However, whether the association is causal or due to confounding factors needs further investigation (18). Another study detected that a higher dietary magnesium intake was associated with a reduced risk of cancer mortality (19). These results collectively suggest that consuming magnesium from dietary sources may be beneficial for reducing CRC mortality, with practical implications for public health. Calcium and magnesium contribute to water hardness. Although cations determine hardness, it may be discussed in terms of permanent (non-carbonate) and temporary (carbonate) hardness. The latter is caused by the presence of dissolved bicarbonate minerals, mainly calcium and magnesium bicarbonate. When dissolved, these minerals yield calcium and magnesium cations (Ca^{2+}, Mg^{2+}) and carbonate-bicarbonate anions (CO_3^{2-} and HCO_3^-). Ca^{2+} and Mg^{2+} cations make the water hard, with hardness measured by CO_3^{2-} and HCO_3^- anions. By approximation, hardness is expressed as equivalents of calcium carbonate per litre (mg $CaCO_3$/L) (20). The World Health Organization (21) defined the following hardness grade (mg $CaCO_3$/L) for hard and soft water: soft (< 60 mg/L), moderately hard (60–120 mg/L), hard (120–180 mg/L), and very hard (≥ 180 mg/L). A few studies hypothesised how drinking hard water could benefit human health (22). Also, the association between hardness levels in drinking water and CRC mortality was investigated, even if the evidence is still scarce (23,24), and more studies need to evaluate the topic further. Considering the above, drinking water rich in calcium, magnesium, and hardness might benefit CRC. However, some studies also reported little benefits, null or non-beneficial effects (25,26), and there is still limited evidence from reviews conducted on their impact on this specific cancer type when their intake comes from drinking water. Therefore, we conducted a systematic review to explore and summarise the impact of calcium, magnesium, and water hardness on CRC mortality.

Methods

This work followed the Cochrane Collaboration (27) and Handbook (28), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (29–31) (Table S1). The protocol was registered in Open Science Framework (OSF) Registries (https://doi.org/10.17605/OSF.IO/5HEVS).

Search strategy and data sources

A thorough literature search was run in January 2025 using the PubMed®, Scopus®, and the Web of Science databases. The literature search was conducted using a predetermined combination of keywords, including drinking water, calcium, magnesium, hardness, and colon/rectal/colorectal cancer. 'Text Word', 'Title/Abstract' and 'MeSH Terms' were the options used in this step. Keywords were then combined using Boolean operators AND/OR. The search strategy was first developed in PubMed (Table S2) and then adjusted for the other databases using SR-Accelerator Polyglot Search Translator (https://sr-accelerator.com/#/polyglot). The reference lists of the retrieved articles were also scrutinised to collect further pertinent studies.

Inclusion and exclusion criteria

Table S3 reports the inclusion and exclusion criteria in line with the Population, Exposure, Outcomes and Study design (PEOS) (32), completed, according to the Cochrane Handbook (28), with time and language filters. Papers were considered eligible if the studies met the following inclusion criteria: (P) adult population (≥ 18 years old); (E) higher calcium, magnesium, and hardness in drinking water; (O) colon, rectal, or colorectal cancer mortality; (S) observational studies. Finally, populations with lower hardness, calcium, or magnesium in drinking water were chosen as comparators/controls. Only papers written in English were considered eligible.

Study selection and data extraction

The title and abstract of the retrieved records were independently screened by two researchers (M.A. and E.F.) to collect potentially pertinent articles. Full text was obtained only for selected reports which met the inclusion criteria. Data were independently extracted from included studies by two authors (M.A. and E.F.) and transferred onto a Microsoft Word® (Redmond, WA, USA) document. When present, the adjusted odds ratio (OR) was preferred over the crude OR. When the OR was not reported in the full text, we obtained it (crude OR) by dividing the odds of the event (colon, rectal, or colorectal cancer deaths) in the exposure group (higher calcium, magnesium, or hardness in drinking water) by the odds of the event in the control or non-exposure group (lower calcium, magnesium, or hardness in drinking water). When more than two thresholds were present, we considered the highest vs. the lowest exposure levels. Also, the 95% confidence interval (CI) was calculated. Pre-configured tables were used to systematically record qualitative and quantitative features extracted from the selected reports. If needed, corresponding authors were contacted by e-mail. Any disagreement was solved through the consultation of a third author (M.M.).

Critical appraisal

The quality evaluation of the selected articles was assessed by two independent researchers (M.A. and E.F.) using the Newcastle-Ottawa Scale (www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The author's disagreement was solved through consultation with a third researcher (M.M.). The total score can range from 0 (the poorest quality) to 9 (the highest quality). Each study's quality score was calculated and reported with the other features extracted from the selected papers.

Results

Literature search

Our electronic searches yielded 133 references, of which 81 remained after duplicate removal (n = 52). First, we screened the titles and abstracts of these records. After excluding articles in languages other than English (n = 4), we identified 77 as potentially eligible and obtained the full text for 75 reports (reports not retrieved, n = 2). After that, 66 reports were excluded for the following reasons: *in vitro*/plant/animal models (n = 24), reviews and meta-analyses (various topics) (n = 13), non-primary data, protocols, letters, position papers, conference proceedings, book chapters (n = 6), different cancer type (n = 4) unrelated topic, different outcome, or lack of a control group (n = 19). At the end of the selection procedure, nine studies were included in the systematic review (Figure 1).

Characteristics of the included studies

Qualitative and quantitative features of the included studies are reported in Tables 1 and 2, respectively. When two studies had the same first author and were published in the same year, we marked one study with the (a) letter, and the other with the (b) letter. All the studies were conducted in Taiwan, China (Asia) and were supported by the National Science Council, Executive Yuan, Taiwan, China. Data were retrieved from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health in all the studies. The case group always consisted of all colon or rectal cancer deaths occurring in subjects aged 50–69 years. In contrast, the control group consisted of all other deaths, excluding those deaths which were associated with colon or rectal cancer.

The first paper was released in 1997 (33), whereas the most recent one was published online in 2011 (34). All the studies were published within two distinct periods: from 1997 to 1999 and from 2010 to 2011. In six studies (23–25,33–35), data were obtained over four years, whereas in three studies (26,36,37) mortality data were retrieved over nine years. In five reports (24,26,33,34,37), the study outcome concerned colon cancer mortality, whereas in four reports (23,25,35,36), the study outcome concerned rectal cancer mortality. The exposure data (calcium and/or magnesium levels or total hardness) were always retrieved from the Taiwan Water Supply Corporation (TWSC) database. Calcium levels were considered in two studies (34,37), magnesium levels in one (26), whereas four studies retrieved data on both minerals

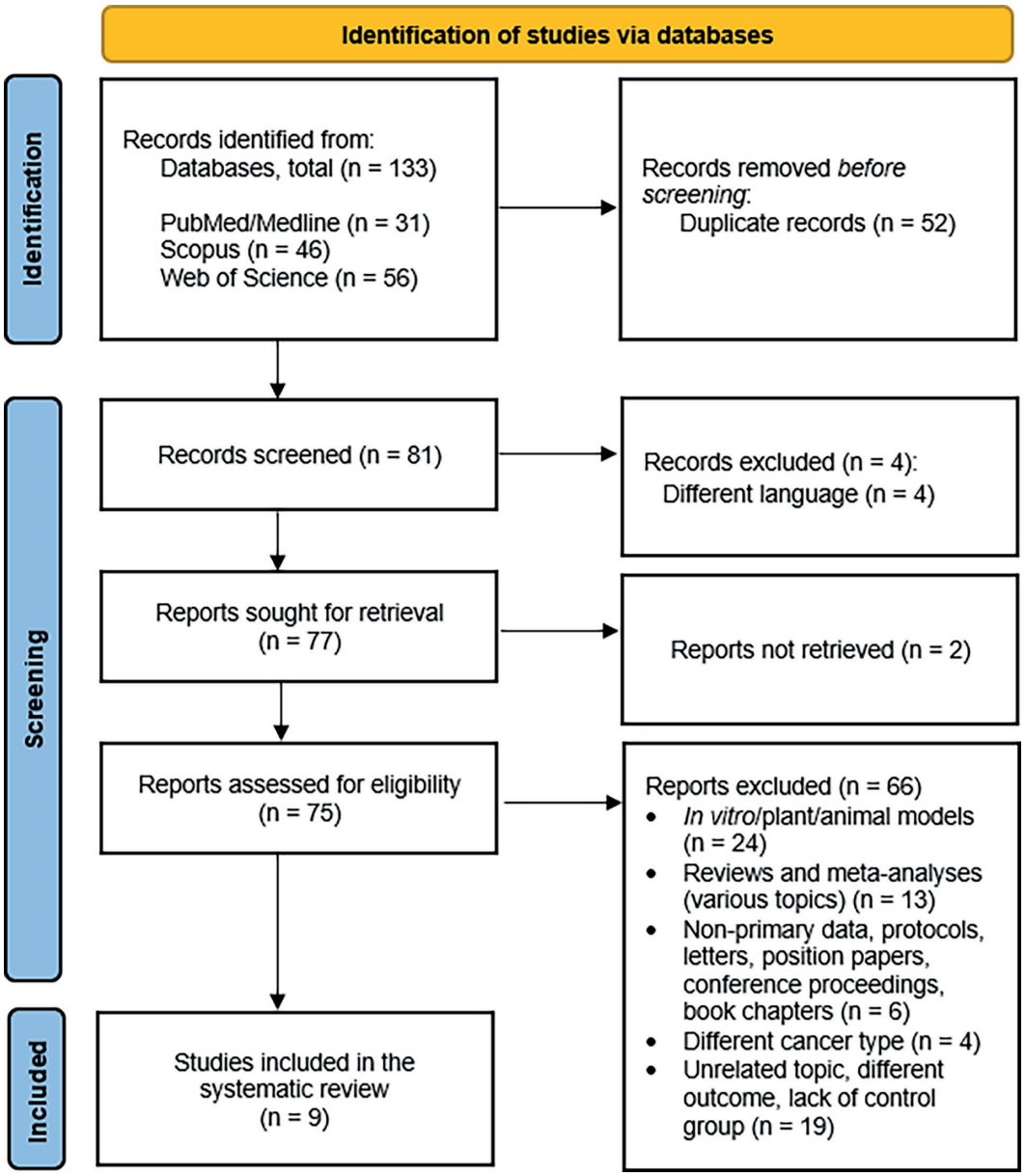

Figure 1. Flow diagram of the selection process according to the PRISMA 2020 statement (31).

(25,33,35,36). No study has considered calcium and magnesium as co-exposures. Hardness ($CaCO_3$) was highlighted in two studies (23,24). When considering calcium in drinking water, selected studies considered different exposure cut-offs. In one study (35), the cut-off was set to 20.2 mg/L; in two studies (36,37), the cut-off was set to 22 mg/L; in one study (33), the cut-off was set to 24.0 mg/L; in two studies (25,34), the cut-offs were set to higher levels (34.6–34.7 mg/L). Also, when considering magnesium in drinking water, selected studies considered different exposure cut-offs. Two studies (26,36) set the cut-off to 5.9 mg/L; in one study (35), the cut-off was set to 7.0 mg/mL; in one study (33) the cut-off was set to 7.3 mg/mL; in one study (25), the cut-off was set to 9.3 mg/mL. When considering drinking water hardness (23,24), the cut-off between exposed and non-exposed subjects was always set to 0–75 mg/mL. The total number of

Table 1. Main qualitative characteristics of the included studies reported chronologically.

Author (year)	Study period	Study design	Disease	Exposure
Chiu et al. (2011) (34)	2003-2007	Case-control (mortality)	Colon cancer	Calcium
Kuo et al. (2011) (26)	1998-2007	Case-control (mortality)	Colon cancer	Magnesium
Chang et al. (2010) (25)	2003-2007	Case-control (mortality)	Rectal cancer	Calcium Magnesium
Kuo et al. (2010a) (36)	1998-2007	Case-control (mortality)	Rectal cancer	Calcium Magnesium
Kuo et al. (2010b) (37)	1998-2007	Case-control (mortality)	Colon cancer	Calcium
Yang et al. (1999) (23)	1990-1994	Case-control (mortality)	Rectal cancer	Hardness
Yang and Chiu (1998) (35)	1990-1994	Case-control (mortality)	Rectal cancer	Calcium Magnesium
Yang and Hung (1998) (24)	1989-1993	Case-control (mortality)	Colon cancer	Hardness
Yang et al. (1997) (33)	1989-1993	Case-control (mortality)	Colon cancer	Calcium Magnesium

subjects ranged from 1972 (23,35) to 7414 (34). According to the Newcastle-Ottawa Scale, five studies received a quality score of 7 (25,26,34,36,37), whereas four of the selected studies received a quality score of 8 (23,24,33,35).

Findings from the selected studies

Calcium in drinking water

Six studies evaluated the effect of calcium in drinking water on CRC mortality risk. Among them, three studies (33,34,37) highlighted a statistically significant protective effect against colon cancer. In particular, Yang et al. (33) calculated an OR of 0.58 with a 95% CI of [0.47–0.73], whereas results yielded by Kuo et al. (b) (37) and Chiu et al. (34) led to an OR of 0.81 [95% CI 0.72–0.91] and 0.86 [95% CI 0.79–0.94], respectively. Three studies (25,35,36) specifically assessed the effect of calcium in drinking water on rectal cancer mortality. One study (35) highlighted a statistically significant protective effect, with an OR of 0.63 [95% CI 0.45–0.87]. The remaining two studies showed an increased risk of death associated with higher calcium concentrations. In one case (36), the effect was statistically significant, with an OR of 1.23 [95% CI 1.04–1.45], in the other study (25), it was not (OR = 1.11 [95% CI 0.98–1.27]).

Magnesium in drinking water

Five studies evaluated the effect of drinking water magnesium on CRC mortality risk. Among them, two studies specifically investigated the impact on colon cancer: Kuo et al. (26) detected a statistically significant protective effect, with an OR of 0.87 [95% CI 0.77–0.98], whereas Yang et al. (33) showed no effect, with an OR of 1.06 [0.85–1.32]. Three studies assessed the effect of magnesium in drinking water on rectal cancer mortality. One study (36) showed a rise in death risk associated with higher magnesium concentrations, leading to a statistically significant effect, with an OR of 1.20 [95% CI 1.01–1.42], while the other studies (25,35) did not present statistical significance (OR = 0.99 [95% CI 0.87–1.13]; OR = 1.11 [0.80–1.54]).

Drinking water hardness

Only two studies checked drinking water hardness on CRC mortality risk. Both detected a statistically

significant protective effect against CRC: data collected by Yang and Hung (24) resulted in an OR of 0.63 [95% CI 0.54–0.75] for colon cancer, and those obtained by Yang et al. (23) resulted in an OR of 0.66 [95% CI 0.53–0.82] for rectal cancer.

Discussion

The current systematic review examined the effect of calcium, magnesium, and water hardness on CRC mortality risk. The results pointed to interesting considerations regarding the effects of exposure to drinking water calcium, magnesium, and water hardness on colon and rectal cancer mortality. Considering calcium exposure on colon cancer outcome, all the studies showed a statistically significant protective effect on the exposed population, whereas calcium exposure did not positively affect rectal cancer mortality outcome (mixed and non-concordant results). Thus, water calcium exposure showed a relevant protective effect on colon cancer taken separately. About 90% of calcium absorption occurs in the small intestine, especially the ileum. However, recent evidence indicates that the colon is a significant site of calcium absorption, contributing to overall calcium homeostasis, particularly when dietary calcium intake is low (38). Indeed, intestinal epithelial calcium channels (transient receptor potential vanilloid 6, TRPV6) have been detected in the human colon (39). Most of the absorption in the large bowel seems to be limited to the cecum and the ascending colon (40), whereas a small or absent calcium absorption has been reported in the distal colon and rectum in both humans and rats (41,42). This difference might explain the decrease in the protective effect when moving from colon to rectum cancer. Calcium has previously been shown to affect such diseases. Indeed, our results partially align with WCRF, which stated that there is strong evidence that consuming dairy products – among the most common sources of calcium – and taking calcium supplements decreases the risk of CRC (8). WCRF pointed out some evidence showing that higher consumption of dairy products might simultaneously increase the risk of prostate cancer, as well (43). This was also confirmed by a recent meta-analytic study (11). The same conclusion was also drawn for diets high in calcium. Still, the relationship was only significant for dairy calcium (43), raising doubts about the large intake of dairy products as 'healthy' sources of calcium. Considering magnesium exposure on colon and rectal cancer outcomes, the results of the studies were mixed and non-concordant, with only one study showing a protective effect in colon cancer. Intestinal magnesium absorption occurs predominantly in the small intestine via a paracellular pathway. Smaller amounts of magnesium are absorbed in the colon, mainly via a transcellular pathway (44), whereas it is not substantially absorbed from the distal colon and rectum (in rats) (41). Analogously to what we observed for calcium, such mechanisms might underlie the results obtained in the selected studies. Considering the above and daily water intake recommendations (45–47), an intake of water rich in calcium strongly contributes to a remarkable percentage of one's physiological daily needs. In addition, it provides a readily available, healthy, and low-cost calcium source, preventing consumers from relying on other, less healthy, more expensive, and fat-rich food sources. Finally, we also investigated the effect of water hardness on CRC mortality risk. According to the selected studies, the positive effect of hardness exposure on colon (n = 1) and rectum (n = 1) cancer outcomes is statistically significant. Overall, water calcium exposure showed a protective effect on colon cancer mortality, suggesting that these water intake features benefit colon cancer outcomes. Conversely, rectal cancer did not appear to benefit from high calcium and magnesium water intake. Water hardness seemed to have protective effects on both colon and rectal cancer outcomes; however, only two studies were available for this specific exposure; thus, results should be interpreted with caution. Some evidence allows us to speculate about the mechanisms which act behind the effects of such minerals on colon and rectal cancer. The interaction between nitrate-nitrogen (NO_3-N) and calcium in drinking water could be a relevant factor, given that, at high NO_3-N levels, low calcium exposure was linked to a higher risk of death from colon (34) and rectal (25) cancer. Similarly, low magnesium levels and high NO_3-N levels in water were linked to a rise (non-significant) in death risk by rectal cancer (25), suggesting that such minerals might partially

Table 2. Main quantitative characteristics of the included studies reported chronologically.

Author (year)	Sample size sex age in years (range)	Disease	Exposure(s)	Cases (n.)	Controls (n.)	OR [95% CI]	Quality score (Newcastle-Ottawa Scale)
Chiu et al. (2011) (34)	7414 subjects M: 4174 (56.3%) F: 3240 (43.7%) 50-69 years old	Colon cancer	$[Ca^{2+}]$ (mg/L) < 34.6 ≥ 34.6	2009 1698	1872 1835	0.86 [0.79–0.94]	7/9
Kuo et al. (2011) (26)	4360 subjects M: 2478 (56.8%) F: 1882 (43.2%) 50-69 years old	Colon cancer	$[Mg^{2+}]$ (mg/L) < 5.9 ≥ 5.9	1202 978	1126 1054	0.87 [0.77–0.98]	7/9
Chang et al. (2010) (25)	3676 subjects M: 2240 (60.9%) F: 1436 (39.1%) 50-69 years old	Rectal cancer	$[Ca^{2+}]$ (mg/L) < 34.7 ≥ 34.7	862 976	911 927	1.11 [0.98–1.27]	7/9
			$[Mg^{2+}]$ (mg/L) < 9.3 ≥ 9.3	805 1033	802 1036	0.99 [0.87–1.13]	
Kuo et al. (2010a) (36)	2212 subjects M: 1358 (61.4%) F: 854 (38.6%) 50-69 years old	Rectal cancer	$[Ca^{2+}]$ (mg/L) < 22.0 ≥ 22.0	488 618	545 561	1.23 [1.04–1.45]	7/9
			$[Mg^{2+}]$ (mg/L) < 5.9 ≥ 5.9	495 611	545 561	1.20 [1.01–1.42]	
Kuo et al. (2010b) (37)	4360 subjects M: 2478 (56.8%) F: 1882 (43.2%) 50-69 years old	Colon cancer	$[Ca^{2+}]$ (mg/L) < 22.0 ≥ 22.0	1227 953	1114 1066	0.81 [0.72–0.91]	7/9
Yang et al. (1999) (23)	1972 subjects M: 1204 (61.1%) F: 768 (38.9%) 50-69 years old	Rectal cancer	$[CaCO_3]$ (mg/L) < 75.0 75.0-150.0 > 150.0	321 322 343	258 312 416	0.66 [0.53–0.82]	8/9
Yang and Chiu (1998) (35)	1972 subjects M: 1204 (61.1%) F: 768 (38.9%) 50-69 years old	Rectal cancer	$[Ca^{2+}]$ (mg/L) ≤ 20.2 22.0-40.8 40.9-79.2	374 311 301	288 332 366	0.63 [0.45–0.87]	8/9
			$[Mg^{2+}]$ (mg/L) ≤ 7.0 7.3-11.6 11.7-41.3	340 326 320	297 320 369	1.11 [0.80–1.54]	
Yang and Hung (1998) (24)	3428 subjects M: 1874 (54.7%) F: 1554 (45.3%) 50-69 years old	Colon cancer	$[CaCO_3]$ (mg/L) < 75.0 75.0-150.0 > 150.0	518 545 651	394 539 781	0.63 [0.54–0.75]	8/9

Author (year)	Sample size sex age in years (range)	Disease	Exposure(s)	Cases (n.)	Controls (n.)	OR [95% CI]	Quality score (Newcastle-Ottawa Scale)
Yang et al. (1997) (33)	3428 subjects M: 1874 (54.7%) F: 1554 (45.3%) 50-69 years old	Colon cancer	$[Ca^{2+}]$ (mg/L) ≤ 24.0 24.4-42.3 42.4-81.0	649 576 489	488 568 658	0.58 [0.47–0.73]	8/9
			$[Mg^{2+}]$ (mg/L) ≤ 7.3 7.4-13.3 13.4-41.3	632 567 515	555 527 632	1.06 [0.85–1.32]	

modify the effects of nitrate exposure on the risk of mortality from such diseases. In addition, an interaction between drinking water total trihalomethanes (TTHM) and water calcium-magnesium intake was hypothesised. When high levels of TTHM in drinking water occurred, low calcium and magnesium exposure were linked to a rise in death risk from colon (26,37) and rectal (36) cancer, suggesting a similar effect to that observed with co-exposure to nitrates. These data, which allow us, at least partially, to formulate hypotheses about the above findings, suggest that water disinfection by-products, in addition to inducing genotoxic effects (48), may also interact with other components, potentially worsening the situation. Some pieces of evidence found a significant inverse relationship between the content of calcium and magnesium in drinking water and the risk of death from breast cancer (49). While successive research on the association between dietary magnesium and the risk of breast cancer led to inconclusive results (50), diets high in calcium are supposed to possibly decrease the risk of premenopausal breast cancer (51). With the above in mind, it sounds reasonable to include calcium-rich drinking water within the nutritional assessment and in nutrition education programs addressed to breast cancer patients, which might also contribute to a further improvement of existing projects (52–54). The present study is affected by some limitations. First, we only included studies published in English, so reporting bias (i.e., language bias) cannot be excluded. No recent studies have investigated these topics, as the most recent was conducted in 2011. Another limitation lies in the varying thresholds that different studies used to define 'high' and 'low' levels of calcium and magnesium. Then, none of the studies included in this systematic review considered calcium and magnesium as co-exposures. Calcium and magnesium share the same homeostatic regulating system and interact with each other in some physio-pathological pathways (55–59). Moreover, in addition to absolute mineral intake, the calcium-to-magnesium intake ratio has been suggested to play a role in CRC onset, treatment, and mortality risk (60–65). For these reasons, future research should also take these aspects into account when examining the effects of exposure to drinking water with varying hardness levels. Furthermore, only two studies (33,35) directly reported OR adjusted for age, sex, and urbanisation level of residence (in (33), the authors also adjusted for magnesium levels in drinking water when analysing calcium exposure and for calcium levels in drinking water when analysing magnesium exposure). Other confounding factors (e.g., dietary calcium and magnesium intake, socioeconomic status, healthcare access, and other environmental exposures) were not considered. In the other cases, due to a lack of individual data, we calculated crude ORs without adjusting for confounding factors. To date, there are no cohort studies or randomised controlled trials (RCTs) investigating these associations, suggesting a research gap that should be addressed with further studies of greater design complexity. Finally, all the studies were conducted in the same geographical area, namely, Taiwan, China. This feature, along with the high heterogeneity, made the implementation of the meta-analysis illogical, as extending the cumulative effects to the general population would be somewhat incoherent. We did not perform the Risk of Bias assessment because, to date, ROBINS-E tool for the Risk of Bias

assessment in observational studies only considers cohort studies and is not suitable for case-control studies (66). Although some studies seem to involve the same population ((24) and (33); (23) and (35); (26) and (37)), data have been checked – and results have been reported – considering distinct exposures (Ca, Mg and $CaCO_3$) taken individually.

Conclusions

In conclusion, this systematic review suggested that higher calcium concentrations in drinking water protect against colon cancer mortality, whereas the effects on rectal cancer mortality seem to be mixed. High water hardness seems to protect against mortality from both cancer types. Before drawing definitive conclusions, further novel, large observational (preferably longitudinal) studies and RCTs should be conducted in other parts of the world to investigate such effects in different ethnic groups, to support the benefits or address inconclusive results.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

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