Dietary magnesium: The magic mineral that protects from colon cancer?

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Magnesium is an essential cation for many important biological functions such as metabolism, muscle contraction, blood pressure, neurological function, to name just a few. Standard Western diets are low in magnesium due to the plethora of refined foods and the often low intake of fruit and vegetables. As a consequence, a modest to mild hypomagnesemia is observed in a large number of individuals [1].

A Korean research group [2] recently conducted a meta-analysis of epidemiological studies aimed at assessing whether magnesium levels in the diet affect the risk of developing cancer. In fact, several observational human studies on the relationship between magnesium intake and the risk of developing specific types of cancer have been conducted and published previously; however, to our knowledge, it is the first meta-analysis evaluating the relationship between the overall cancer incidence and dietary magnesium.

Among the large number of studies (1,503) published up to 2012, 13 observational human studies were considered suitable for the given meta-analysis. These studies, including 1,236,004 subjects, investigated the effect of dietary magnesium, assessed by a validated food frequency questionnaire, on the risk of developing specific tumors: colorectal cancer, four studies; lung cancer, three studies; pancreatic cancer, three studies; and renal, esophageal, and bladder cancer, one study each. Data on the effects of magnesium supplementation, if present, were excluded from the meta-analysis, due to possible confounding effects that could result from variations in the content, duration, and dosage of the supplementation regime. Random-effects model meta-analysis of the selected studies revealed that the relative risk (RR) of the high dietary magnesium intake group was 0.801 (95% CI: 0.664-0.966) compared to the low dietary magnesium intake group, which corresponds to a 19.9% reduction in cancer incidence. These results suggest that dietary magnesium intake has a significant protective effect against carcinogenesis in general, which fits well with the multifaceted relationship between magnesium and cancer [3]. In particular, magnesium modulates DNA repair systems, as well as inflammation and oxidative stress, thus magnesium deficiency could promote genetic instability and contribute to tumor initiation [4]. Furthermore, altered expression of magnesium transporters has been implicated in the initiation and progression of several types of cancer [5]; in particular the transient receptor potential melastatin channel (TRPM7), the gatekeeper of systemic magnesium balance, has been proposed as a potential diagnostic and prognostic marker of tumor progression [6].

The subgroup meta-analysis in [2] showed that the protective effect of dietary magnesium against cancer reached significance in particular in female populations (RR = 0.839; 95% CI: 0.715-0.985),
colorectal cancer (RR = 0.775; 95% CI: 0.655-0.919), and Western populations (RR = 0.795; 95% CI: 0.639-0.990).

We can speculate on the sex specificity shown for the inverse correlation between magnesium intake and the colorectal cancer incidence. The recommended daily magnesium intake is 420 mg/day for male adults and 320 mg/day for female adults, whereas the average daily magnesium intake is reported to be 278-352 mg/day in the male population and 237-326 mg/day in the female population in the United States [2]. Thus, in both cases, average intake appears to be below the recommended amount: however, the discrepancy between RDA and actual intake seems to be less marked in females, which may cause a less severe magnesium deficiency and account for the better protection observed in Ko's study [2]. This observation casts additional emphasis on the definition of the recommended daily magnesium intake, and its importance for human health. More importantly, differences in hormonal profiles are the main factors that might explain differences between the sexes. In this context, it must be noted that TRPM6 is regulated at the level of transcription, plasma membrane availability, and activity by numerous factors, including EGF, insulin, and most notably, estrogens [7]. In particular, estrogens increase TRPM6 mRNA expression [8], which could result in improved magnesium absorption from dietary intake.

Subgroup meta-analysis by cancer type in [2] revealed that there was a statistically significant cancer risk reduction of 22.5% for colorectal cancer, which was the most frequently studied. No significant statistical association between dietary magnesium intake and lung cancer, or pancreatic cancer was observed. The authors argued that lack of significance of the latter associations might be due to the limited number of studies analyzed. Inverse association between dietary magnesium intake and colorectal cancer risk has already been suggested by several previous meta-analysis studies. One included 333,510 participants with 7,435 colorectal cancers from seven prospective cohort studies, and found an RR for the highest versus the lowest magnesium intake of 0.81 [9]. In another similar work it was concluded that higher magnesium intake seems to be associated with a modest reduction in the risk of colorectal cancer, in particular colon cancer [10]. Another meta-analysis indicated that every 100-mg/d increase in magnesium intake was associated with 13% lower risk of colorectal adenomas and 12% lower risk of colorectal cancer [11].

In order to explain the protective effects of magnesium demonstrated specifically for colorectal cancer, we can put forward several hypotheses. First of all, the direct contact between dietary magnesium and colonic mucosa assures exposure to the highest magnesium concentrations. This could easily translate into more efficient local anti-inflammatory and anti-oxidant effects [12]. Second, colonic mucosa plays a key role in magnesium absorption and homeostasis within the whole body. Magnesium is absorbed in the intestine via two main routes: paracellular transport, occurring mostly in the small intestine through still unidentified tight junction protein complexes, and transcellular transport, taking place in the cecum and colon through ion channels belonging to the transient receptor potential melastatin family, namely TRPM6 and TRPM7 [7]. Together with renal re-absorption, these mechanisms control magnesiumemia, and guarantee magnesium-dependent processes (e.g. insulin activity, antioxidant reactions including LDL-oxidation, DNA oxidative damage, muscle contraction, angiogenesis, etc.).

The idea that magnesium may protect against colorectal carcinogenesis at an early stage is supported by an association study in humans [13]. Magnesium intake was found to be inversely associated with the risk of developing colorectal adenomas and hyperplastic polyps, which may eventually evolve into carcinomas. Interestingly, a genetic polymorphism in TRPM7 significantly interacted with Ca:Mg intake in relation to the risk of either adenomatous or hyperplastic polyps. Carriers of the Thr1482Ile allele, which confers greater sensitivity to channel inhibition, were at greater risk, particularly if they consumed diets with a high Ca:Mg intake. Several experimental findings support the hypothesis that TRPM7 may be involved in regulating the balance between Mg$^{2+}$ and Ca$^{2+}$ [13], and that this could be critical for initiation/progression of cancer [14]. Altogether, it appears uncontroversial that magnesium intake and magnesium channels are important determinants of colon health; the Ca$^+$/Mg$^{2+}$ ratio could represent another crucial factor that warrants further investigation. In addition, genetic variants of TRPM6 and TRPM7 contributing to the risk of cancer need to be thoroughly analyzed, especially in view of subgroup
meta-analysis by country showing significant protection by magnesium in Western populations [2].

It is well known that inflammation creates a favorable microenvironment for tumor development, and chronic inflammation is strongly associated with several human cancers [15]. In the context of colorectal cancer, effects of magnesium on inflammatory responses and mediators are of particular interest, since inflammatory bowel disease (IBD) is widely accepted as one of the most important risk factors leading to colorectal cancer [16]. IBD is a chronic inflammatory condition of the gastrointestinal tract that could be exacerbated by mucosal deficiency of magnesium, as this can lead to activation of the NFκB pathway, secretion of proinflammatory cytokines including IL6, TNFα and IFNγ, stimulation of NMDA receptor signaling and substance P release [17]. Interestingly, in mice drinking water supplemented with different amounts of magnesium, inflammation-associated colon carcinogenesis was significantly reduced at all doses of magnesium [18]. On the other hand, as the colon is the main gateway for systemic magnesium absorption, it is not surprising that IBD, and the consequent damage to the intestine, is often associated with hypomagnesemia [17]. In addition, IBD patients, like other patients with gastrointestinal disorders, may spontaneously reduce food intake, avoiding in particular those foods that are richer in magnesium, such as vegetables, nuts and fruit; this may happen especially in active phases of the disease, when conversely it would be advisable to consume an even higher intake. Last but not least, it has been shown that Mg deficiency, independently of any other changes in nutrient intake, modulates the concentration of bifidobacteria in the gut, a phenomenon that may, time-dependently, affect inflammation and metabolic disorders in mice [19].

Intriguingly, in the search for molecular determinants that could be used for diagnostics and screening of IBD versus non IBD-colitis cases and controls, it was found that in IBD cases, TRPM6 expression increased in peripheral leukocytes, while it decreased in the lamina propria of the inflamed mucosa. The authors justified their findings reasoning that leukocytes may change phenotype in the inflamed mucosa, and lack of TRPM6 expression in the mucosa may contribute to the symptoms associated with hypomagnesemia in IBD [20].

We believe that the relationship between magnesium homeostasis and IBD is a very interesting issue, and has so far received less attention than it deserves. IBD represents an intriguing prototype of disorders associated with alterations of magnesium homeostasis, as it may interconnect several aspects: dietary intake, absorption, immuno-modulatory properties, dietary and inflammatory regulation of ion channels, tumor initiation/progression and healing processes. Clarifying the role of magnesium and magnesium channels in maintaining a healthy immune system and intestinal mucosa might contribute to the understanding of the pathogenesis of IBD and inflammation-associated cancer. Most importantly, this research may promote a more conscious use of magnesium in health promotion as well as in disease treatment. Ultimately, this may lead to the development of effective magnesium supplementation strategies, and more generally, novel pharmacological approaches, not just for controlling inflammation, but also for reducing the risk of colon cancer associated with colonic inflammation.

Disclosure


References


