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In: "Nutrition for the Middle Aged and Elderly"
Editor:
N. E. Bernhardt and A. M. Kasko
ISBN:
978-1-60456-146-3
2008

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In: Nutrition for the Middle Aged and Elderly ISBN: 978-1-60456-146-3
Editors: N. E. Bernhardt, A. M. Kasko, pp. 271-284

Chapter IX

Serum Magnesium and Cancer Mortality

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Dedication

This chapter is dedicated to my parents, who both died of cancer far too young, and to my wife who is a cancer survivor. – CJE.

Abstract

The association of serum magnesium with cancer mortality was investigated prospectively using the Atherosclerosis Risk in Communities (ARIC) Study. Black (N=3,898) and nonblack (N=10,534) participants, aged 45-64 at baseline, were analyzed separately. In a Cox's regression adjusted for gender, age, body mass index, exercise, education, number of cigarettes currently smoked, and smoking history, nonblack participants with serum magnesium $\leq$1.4 meq/l had a hazard ratio of 2.72 (95% CI 1.40-5.29) for all-cancer mortality compared to persons with serum magnesium $\geq$1.9 meq/l. When nonblack participants were classified as $\leq$1.6 meq/l versus $\geq$1.7 meq/l, low serum magnesium had a hazard ratio of 1.53 (95% CI 1.19-1.97) for all-cancer mortality. Significant inverse relationships between nonblack participants' serum magnesium and two types of cancer mortality were found. First, an association with mortality due to malignant neoplasm of respiratory/intrathoracic organs, and second an association with all other types of cancer mortality. For black participants there was no association of serum magnesium and all-cancer mortality. This pattern of a relationship with serum magnesium among nonblack participants, but no association among black participants

was similar to previously published research on the development of diabetes and serum magnesium in the ARIC Study.

Introduction

Recent biologic and epidemiologic evidence strongly supports a significant role for magnesium in human health, and in particular, in the relationship between hypertension and inflammation [1-3]. Further, in light of recent evidence that 77% of adults and 84% of adults with hypertension plus inflammation have magnesium intake below the recommended daily allowance (RDA) [4-5], evaluating the possible impact of magnesium intake on human health and cancer is clearly timely.

The association between magnesium and the body's inflammatory response may have implications for the association between magnesium and subsequent cancer. As early as two decades ago, Bloom [6] demonstrated the development of inflammation in the coronary arteries of hamsters fed a magnesium-deficient diet. Affected arteries showed endothelial cell hyperplasia and pleomorphism, chronic inflammation of the media and adventitia, and fibrinoid necrosis. The author concluded that this inflammation response was a significant factor to be considered in the pathophysiology of magnesium-poor diets.

Chronic inflammation has been linked to several solid malignancies, including esophageal, gastric, liver, pancreatic, renal and prostatic cancers [7-9]. Possible mechanisms by which inflammation may contribute to carcinogenesis include elaboration of inflammatory cytokines and growth factors that favor tumor cell growth, induction of cyclo-oxygenase-2 in macrophages and epithelial cells; and promotion of oxidative stress [10].

In support of the inflammatory model linking cancer and magnesium, evidence of inflammation has been found in magnesium-deficient rat models [11]. More recently, Maier [12] found that low serum magnesium concentrations impact the inflammatory response by affecting pro-inflammatory cytokines, such as up-regulation of interleukin-1 (IL-1) and serum vascular adhesion molecule (sVCAM-1). Magnesium deficiency in rats is also associated with an increase in serum levels of tumor necrosis factor-α [13].

In humans, magnesium operates in many enzyme systems, including acting as the rate-limiting enzyme in the cholesterol biosynthesis sequence that is targeted by HMG-CoA reductase inhibitor drugs (statins), which are known to lower systemic inflammation [14]. In this context, magnesium has been shown to inhibit proliferation and migration of vascular smooth muscle cells and macrophages. This effect offers one of several possible mechanisms for the anti-inflammatory effects of magnesium.

Recent studies add human epidemiologic evidence that magnesium may play a role in inflammation. Guerrero-Romero et al. [15] have investigated the association of serum magnesium levels with c-reactive protein (CRP), an inflammatory biomarker, and found the likelihood of having elevated CRP, after adjustment for demographic and other factors, was 2.11 (1.23-3.84) for those in the lowest quintile of serum magnesium compared to the highest. Other researchers have found that magnesium intake and inflammation are inversely related [16, 17]. Inflammation has been theorized to be an important component of carcinogenesis and CRP levels have been associated with cancer risk [18-20].

In a recent study by King et al [4], adults who consumed <50% of the recommended daily allowance (RDA) of magnesium were more likely to have elevated CRP than adults who consumed ≥ RDA (Odds Ratio [OR] = 1.75, 95% CI 1.08-2.87). In a second cross-sectional study, it was found that magnesium supplementation lowers the likelihood of elevated CRP in people with low dietary magnesium intake by 22% [5]. This observation suggests that magnesium supplementation may be a useful strategy for reduction of inflammation. The study also provides important epidemiologic support for the idea that magnesium itself, rather than some component of magnesium-containing food, is responsible for the decreased inflammation.

Magnesium's impact on oxidative stress is another possible mechanism for the association between magnesium and cancer. Several components of oxidative metabolism are dependent upon dietary micronutrients [21]. Accumulating experimental evidence supports the idea that magnesium deficiency promotes an immuno-inflammatory reaction and increased oxidative stress that can damage cells [22-24]. In addition, magnesium-deficient rats demonstrate an increased susceptibility to oxidative stress in organ tissues including the liver [25].

A recent study was undertaken to examine the hypothesis that magnesium deficiency accentuates oxidative stress in experimental rats [26]. Electrically stimulated rat papillary muscle was used for recording the contractile variation. Biochemical variables were assayed in Langendorff-perfused rat hearts. Hydrogen peroxide was used as the source of reactive oxygen species. The negative inotropic response to hydrogen peroxide was significantly higher in Mg deficiency (0.48 mmol Mg/L) than in Mg sufficiency (1.2 mmol Mg/L). Hydrogen peroxide induced an enhancement of oxidative stress in the presence of Mg deficiency.

Evidence in humans suggests that a magnesium-rich diet may enhance antioxidant capacity [27]. In Lopes' study, 24 individuals were studied on their usual diets and after following a magnesium-rich diet and a low-antioxidant diet in random sequence for 4 weeks each. Acute oxidative stress was induced by a 4-hour infusion of intralipid and heparin. Ferric-reducing activity of plasma (FRAP) and plasma F2-isoprostanes were measured as biomarkers of antioxidant capacity and oxidative stress, respectively. F2-isoprostanes increased on the low-antioxidant diet but not in individuals on the magnesium-rich diet. Thus, the magnesium-rich diet made participants more resistant to oxidative stress. In another study, 93 patients with unexplained chronic fatigue were evaluated for magnesium status and oxidant status. Mg deficient patients (47%) had lower total antioxidant capacity in plasma ($p=0.007$) than non-Mg deficient patients.

Magnesium is an abundant element in the human body and is involved in a wide range of metabolic pathways. Magnesium is vital to DNA replication, genomic stability, apoptosis, and cell membrane integrity [28]. Nuclear magnetic resonance spectroscopy has revealed that magnesium is crucial for stabilizing the secondary and tertiary structure of DNA [29], and magnesium protects DNA from oxidative damage [30]. Magnesium's effect on DNA underscores the interest between magnesium and cancer. Magnesium appears to be protective at the early stages of carcinogenesis, while it promotes growth of existing tumors at later stages [13, 31]. Data from animal studies indicate metastases are promoted by low

magnesium levels [31]. Hence, studies of magnesium and cancer mortality may have different results than studies of diagnoses of cancer.

The studies reviewed here deal with all-cancer mortality [32, 33], specific cancer mortality [32, 34-44], and specific cancer morbidity [45-48]. Only one study has measured serum magnesium [33] and three have looked at magnesium intake using a food frequency questionnaire [46-48] the other studies deal with magnesium in drinking water or total hardness of drinking water. Magnesium intake from water represents perhaps 10% of total intake, but magnesium in water is thought to be more easily absorbed than magnesium in food [41]. Water hardness is an indicator of calcium and magnesium content of the water.

Colorectal cancer has been studied more than other types of cancer. Larsson et al. [46] looked at magnesium intake and colorectal cancer morbidity in a cohort study with 14.8 years of follow-up. They found the highest quintile of magnesium intake had a relative risk of 0.59 (95% CI 0.40-0.87) compared to the lowest quintile. Folsom et al. [47] found magnesium intake was not related to colorectal cancer morbidity among Iowa women in a cohort study with 17 years of follow-up. However, when looking specifically at colon cancer, they did find a significant inverse relationship between magnesium intake and colon cancer morbidity. Van den Brandt et al. [48] found magnesium intake was not associated with colorectal morbidity in a case-cohort study with 13.3 years of follow-up. They did find a significant inverse relationship between magnesium intake and colon cancer morbidity or proximal colon cancer morbidity among persons with body mass index $\geq$25 kg/m^2. Looking at magnesium in drinking water, Yang and Chiu [37] found no relationship with rectal cancer mortality in a case-control study conducted in Taiwan. Similarly, Yang et al. [34] found no relationship between magnesium in drinking water and colon cancer mortality. The results of two other case-control studies, also conducted in Taiwan, showed significant inverse relationships between total hardness of drinking water and colon cancer mortality [36] or rectal cancer mortality [38].

In addition to magnesium and colorectal cancer, magnesium and breast cancer, prostate cancer, esophageal cancer, liver cancer, ovarian cancer, and gastric or stomach cancer have been studied. Yang et al. [41] found a significant inverse relationship between magnesium in drinking water and breast cancer mortality in a case-control study conducted in Taiwan. Similarly, Yang et al. [40] found a significant inverse relationship between magnesium in drinking water and prostate cancer mortality. Both total hardness and magnesium content of drinking water have been studied with respect to esophageal cancer mortality. Yang et al. [39] found soft water had an odds ratio of 1.42 (95% CI 1.22-1.66) for esophageal cancer mortality compared to hard water. More specific to the question of magnesium, Yang et al. [42] found magnesium in drinking water to be inversely related to esophageal cancer mortality. Using Bayesian modeling, Tukiendorf and Rybak [45] found magnesium in drinking water to be inversely related to liver cancer morbidity in Poland. In Taiwan, Yang et al. [43] found no relationship between magnesium in drinking water and liver cancer mortality. In another case-control study ovarian cancer mortality was found to be inversely related to magnesium in drinking water [44]. In Japan, Sakamoto et al. [32] studied all-cancer mortality and stomach cancer mortality in relation to magnesium in drinking water. They found no significant relationship for all-cancer mortality, but significant inverse relationship, via a covariate analysis, for magnesium in drinking water and stomach cancer mortality.

Another case-control study from Taiwan showed a significant inverse relationship between magnesium in drinking water and gastric cancer mortality [35]. Taken together, these studies show an inverse relationship between magnesium and a wide variety of specific cancer mortalities.

The only study using the best measure of magnesium status, that is serum magnesium, is a cohort study with 18 years of follow-up [33]. The Paris Prospective Study 2 is a cohort of 4,035 men age 30-60 years at baseline. There were a total of 176 deaths due to cancer during follow-up. Leone et al. [33] found the highest quartile of serum magnesium had a relative risk of 0.5 (95% CI 0.3-0.8) for all-cancer mortality compared to the lowest quartile.

The purpose of this study is to assess the role of race as a factor determining the association, or lack of association, between serum magnesium and cancer mortality. None of the studies preceding ours have evaluated the association of serum magnesium and all-cancer mortality in an African American cohort. We compare and contrast the relationship for the African American participants with that of the mostly Caucasian, nonblack participants of the Atherosclerosis Risk in Communities Study. Where we find an association between serum magnesium and all-cancer mortality we further explore the nature of the relationship for two types of cancer mortality.

Methods

The Atherosclerosis Risk in Communities (ARIC) Study is a cohort of 15,792 participants aged 45 to 64, from four US communities. The locations included are Forsyth County, NC; Jackson, MS (African Americans only), the suburbs of Minneapolis, MN; and Washington County, MD. In the public-use data set, participants are classified as either nonblack or black. The nonblack participants are mostly Caucasians, but include 14 American Indians and 34 Asian participants. The baseline examination (Visit 1) was in 1986-89 and follow-up examinations were in 1990-92 (Visit 2), 1993-95 (Visit 3), and 1996-98 (Visit 4). We conducted a longitudinal analysis using information from Visit 1 to classify participants and then following them to December 31, 1998.

We defined 5 smoking history categories using interview information from Visit 1. Participants were first classified as never, former or current smokers. Former and current smokers were then further classified by response to the question: “On the average of the entire time you smoked, how many cigarettes did you usually smoke per day?” Heavy smokers were defined as those who had smoked 15 or more cigarettes per day, and light smokers as those who had smoked less than 15 cigarettes per day. We used a cut-off of 15 cigarettes per day to make our results comparable to Godtfredsen et al. [49] and because 15 cigarettes per day is close to the mean for former and current African American smokers in the ARIC Study.

Serum magnesium level was measured using the metallochromic dye calmagite (1-[1-hydroxy-4-methyl-2-phenylazo]-2-naphthol-4-sulfonic acid), based on the method of Gindler and Heth [50]. Magnesium was measured to the nearest 0.1 meq/l. The coefficient of variation was 3% for specimens blindly sent to the laboratory 1 week apart [51]. Serum magnesium was classified in two ways, first as $\leq$1.4, 1.5, 1.6, 1.7, 1.8 and $\geq$1.9 meq/l, the

finest increments possible, and second as two categories, $\leq$1.6 and $\geq$1.7 meq/l (split close to the median). We classified magnesium in two ways because it was not possible to use quartiles or quintiles with 0.1 meq/l increments.

We used gender, age, body mass index, exercise and education as control variables due to their associations with cancer and mortality. Body mass index (BMI) was calculated from weight and height measurements as kg/m^2. Exercise was characterized using a sports index derived from answers to a modified version of a questionnaire developed by Baecke et al. [52]. The index was semicontinuous and ranged from 1 (low) to 5 (high). The sports index was a sum of the yearly frequency, weekly duration, and intensity (low, medium, or high) of up to four self-reported sport activities, plus answers to three additional questions about self-rated amount of leisure time activity compared with others of the same age, frequency of sweating, and general frequency of sport play [53]. Exercise physiology research assistants used standard references to assign intensity codes to the types of sports or exercises [54]. Education was classified as three categories: 1) 11 years of schooling or less, 2) High school graduate or vocational school, and 3) College or graduate school or professional school.

To account for current smokers quitting at a later date, and former smokers who resumed smoking at a later date, we included the current number of cigarettes per day a participant smoked as a time-dependent control variable. The current number of cigarettes smoked per day at Visits 1 through 4 was used to create this variable. If a participant was not smoking at a particular visit, the value of this variable was 0 for that time interval.

Participants who died of cancer during the first three years following baseline were excluded from our analyses. These persons may have had undiagnosed cancer at Visit 1, which could introduce misclassification bias due to the association between cancer and hypomagnesaemia.

Our cohort consisted of 14,432 participants age 45-64 at baseline. Events were classified as either all-cancer mortality, mortality due to malignant neoplasm of respiratory and intrathoracic organs (*International Classification of Diseases, Ninth Revision* codes 160-165), or other types of cancer mortality. We excluded from our cohort 873 participants who reported a previous diagnosis of cancer, 90 persons who died of cancer during the first three years following baseline, 206 participants missing magnesium tests, and 191 persons missing smoking, BMI, exercise or education variables. In addition to undergoing clinical examinations, participants were contacted annually to determine their follow-up status. Of the 14,432 persons in our cohort, 1,209 died before December 31, 1998. The remainder had a mean follow-up time of 10.4 years, with the minimum follow-up being 6 years.

We used the statistical package SAS (Statistical Analysis System, Cary, North Carolina) for all analyses. Adjusted Cox's regressions were performed by race. There were 3,898 black participants and 10,534 nonblack participants included in our analyses. Also, there were 131 cases of all-cancer mortality among black participants and 251 cases of all-cancer mortality among nonblack participants.

Results

Demographic data about the participants enrolled in this study are shown in Table 1. A total of 7.8% of the nonblack participants and 21.0% of the black participants had serum magnesium concentrations ≤1.4 meq/l.

Table 1. Demographics of nonblack and black participants

	Nonblack	Black
Serum Magnesium (meq/l) (%)		
≤1.4	7.8	21.0
1.5	14.8	20.8
1.6	26.1	25.3
1.7	27.2	18.3
1.8	16.3	9.9
≥1.9	7.8	4.6
Education (%)		
≤11th Grade	17.1	41.5
High School or Vocational School	45.3	28.2
College or Professional School	37.6	30.2
Smoking (%)		
Never	40.4	47.1
Former Light Smoker	10.4	12.2
Former Heavy Smoker	25.1	11.2
Current Light Smoker	4.6	14.0
Current Heavy Smoker	19.5	15.5
Age (yr) [1]	54.2 (5.7)	53.4 (5.8)
Body Mass Index (kg/m^2)[1]	27.0 (4.9)	29.6 (6.1)
Sports Index[1]	2.5 (0.8)	2.2 (0.7)
[1]Mean (Standard Deviation)		

Results of our Cox's regressions differed substantially between nonblack and black participants. Serum magnesium ≤1.4 meq/l had a hazard ratio of 2.72 (95% CI 1.40-5.29) compared to serum magnesium ≥1.9 meq/l for all-cancer mortality among nonblack participants (Table 2). For black participants, serum magnesium ≤1.4 meq/l had a hazard ratio of 1.36 (95% CI 0.53-3.49) compared to serum magnesium ≥1.9 meq/l for all-cancer mortality (Table 3). The difference between nonblack and black participants was due to a high rate of all-cancer mortality among black participants regardless of magnesium level. For serum magnesium ≥1.9 meq/l there were 2.0 cases per 1,000 person-years among nonblack participants and 4.1 cases per 1,000 person-years among black participants.

When the data for nonblack participants was split nearly in two, 5,133 participants with serum magnesium ≤1.6 meq/l and 5,401 participants with magnesium ≥1.7 meq/l, the hazard

ratio for all-cancer mortality was 1.53 (95% CI 1.19-1.97) for serum magnesium ≤1.6 meq/l compared to serum magnesium ≥1.7 meq/l.

Table 2. Adjusted Cox's regressions using serum magnesium to predict all-cancer mortality among nonblack participants[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Magnesium[3] (meq/l)			
≤ 1.4	2.72	1.40-5.29	5.9
1.5	1.77	0.93-3.38	3.6
1.6	1.82	0.99-3.34	3.8
1.7	1.28	0.68-2.38	2.7
1.8	1.38	0.72-2.64	2.9
≥ 1.9	1.00	---	2.0
Magnesium[4] (meq/l)			
≤ 1.6	1.53	1.19-1.97	4.1
≥ 1.7	1.00	---	2.7

[1] Adjusted for number of cigarettes smoked per day at most recent visit, smoking history, gender, age, body mass index, exercise and education.
[2] Calculated excluding the first three years of follow-up.
[3] Serum magnesium in six categories.
[4] Serum magnesium in two categories.

Table 3. Adjusted Cox's regressions using serum magnesium to predict all-cancer mortality among black participants[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Magnesium[3] (meq/l)			
≤ 1.4	1.36	0.53-3.49	6.5
1.5	1.00	0.38-2.64	4.3
1.6	0.90	0.35-2.35	4.2
1.7	0.96	0.36-2.55	4.3
1.8	1.67	0.62-4.48	7.1
≥ 1.9	1.00	---	4.1
Magnesium[4] (meq/l)			
≤ 1.6	0.92	0.64-1.32	4.9
≥ 1.7	1.00	---	5.1

[1] Adjusted for number of cigarettes smoked per day at most recent visit, smoking history, gender, age, body mass index, exercise and education.
[2] Calculated excluding the first three years of follow-up.
[3] Serum magnesium in six categories.
[4] Serum magnesium in two categories.

Table 4. Adjusted Cox's regressions using serum magnesium to predict mortality due to malignant neoplasm of respiratory and intrathoracic organs among nonblack participants[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Magnesium[3] (meq/l)			
≤ 1.4	3.06	0.83-11.34	1.6
1.5	2.54	0.73-8.86	1.3
1.6	3.09	0.95-10.10	1.6
1.7	1.70	0.50-5.75	0.9
1.8	1.34	0.36-4.96	0.7
≥ 1.9	1.00	---	0.5
Magnesium[4] (meq/l)			
≤ 1.6	1.97	1.27-3.06	1.5
≥ 1.7	1.00	---	0.8

[1] Adjusted for number of cigarettes smoked per day at most recent visit, smoking history, gender, age, body mass index, exercise and education.
[2] Calculated excluding the first three years of follow-up.
[3] Serum magnesium in six categories.
[4] Serum magnesium in two categories.

Table 5. Adjusted Cox's regressions using serum magnesium to predict cancer mortality other than respiratory/intrathoracic organ cancer mortality among nonblack participants[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Magnesium[3] (meq/l)			
≤ 1.4	2.56	1.18-5.53	4.3
1.5	1.50	0.70-3.21	2.4
1.6	1.38	0.67-2.84	2.2
1.7	1.14	0.55-2.36	1.8
1.8	1.40	0.66-2.97	2.2
≥ 1.9	1.00	---	1.5
Magnesium[4] (meq/l)			
≤ 1.6	1.34	0.98-1.82	2.6
≥ 1.7	1.00	---	1.9

[1] Adjusted for number of cigarettes smoked per day at most recent visit, smoking history, gender, age, body mass index, exercise and education.
[2] Calculated excluding the first three years of follow-up.
[3] Serum magnesium in six categories.
[4] Serum magnesium in two categories.

These results indicate a possible role for magnesium in cancer mortality among the nonblack participants regardless of how the data are categorized. To further investigate magnesium and specific types of cancer mortality we conducted two additional analyses of nonblack participants. In the first analysis (Table 4) we looked at mortality due to malignant

neoplasm of respiratory and intrathoracic organs. Using six categories of serum magnesium the results were not significant due to the limited number of cases being analyzed (86 cases). However, when the data were divided into two classes, serum magnesium $\leq$1.6 meq/l had a hazard ratio of 1.97 (95% CI 1.27-3.06) compared to serum magnesium $\geq$1.7 meq/l for mortality due to malignant neoplasm of respiratory and intrathoracic organs. For nonblack cancer mortality other than respiratory/intrathoracic organ cancer mortality, serum magnesium $\leq$1.4 meq/l had a hazard ratio of 2.56 (95% CI 1.18-5.53) compared to serum magnesium $\geq$1.9 meq/l (Table 5). These results indicate magnesium is associated with both respiratory and intrathoracic organ cancer mortality, and other types of cancer mortality among nonblack participants.

Conclusion

Relatively few studies have looked at magnesium and all-cancer mortality. We found inverse relationships between serum magnesium and all-cancer mortality, serum magnesium and mortality due to malignant neoplasm of respiratory and intrathoracic organs, and serum magnesium and cancer mortality other than respiratory/intrathoracic organ cancer mortality, among nonblack participants. There was no relationship between serum magnesium and all-cancer mortality for black participants. This pattern of significant results for the nonblack participants and nonsignificant results for black participants was also observed in a study of serum magnesium and incidence of diabetes conducted using the ARIC Study [55]. In our study, black participants had high rates of all-cancer mortality regardless of serum magnesium levels. The difference between blacks and nonblacks may be due to higher fibrinogen levels among blacks, which has been shown to be associated with cancer mortality, particularly among African Americans [56]. Our results are consistent with those of Leone et al. [33], who evaluated the Paris Prospective Study 2, and confirm a number of studies of magnesium in drinking water and cancer mortality. More studies of magnesium and cancer morbidity are needed as our results, and those of Leone et al. [33], may be due to the promotion of metastases by low levels of magnesium [31].

Acknowledgments

The Atherosclerosis Risk in Communities (ARIC) Study is conducted and supported by the NHLBI in collaboration with the ARIC Study Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the ARIC Study or the NHLBI.

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