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Does a higher ratio of serum calcium to magnesium increase the risk for postmenopausal breast cancer?

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SUMMARY

Breast cancer is the most commonly diagnosed cancer among United States (US) women. Established risk factors explain only about 13% of breast cancer incidence among women in the US. Thus, the cause of most cases of breast cancer remains unknown. In postmenopausal women, serum calcium (Ca) and serum magnesium (Mg) play an important role in skeletal health, cell proliferation and cancer. Mg is essential for DNA duplication and repair and Mg deficiency favors DNA mutations leading to carcinogenesis. Dietary intake of Mg in the US is less than the recommended amount, and the deficit is more pronounced in older individuals where gastrointestinal and renal mechanisms for Mg conservation are not as efficient. Furthermore, healthy postmenopausal women are frequently recommended to take supplemental Ca, but not Mg and vitamin D to maintain bone and overall health. Most women with hormone sensitive breast cancer are recommended to take aromatase inhibitors, which causes bone loss and thus are generally prescribed Ca and vitamin D, but not Mg. Although the association between serum Ca and breast cancer risk remains controversial, we hypothesize that this may be because Mg levels have not been accounted for. Mg level directly influences transient receptor potential melastatin 7 (TRPM7) related Ca influx, calcium–adenosine triphosphatase (Ca–ATP) levels, and cell proliferation, and thereby could lead to cancer. Thus a high serum Ca/Mg ratio is more appropriate and alterations in this ratio could lead to increased development of new and recurrent breast cancer.

Introduction

This paper suggests that a high serum Ca:Mg ratio may be a risk factor for postmenopausal breast cancer. A brief description of the epidemiology of breast cancer is followed by the evidence for the hypothesis.

Breast cancer epidemiology

Breast cancer is the most commonly diagnosed cancer among United States (US) women with an estimated 192,569 new cases diagnosed in 2009. Mortality from breast cancer ranks second only to lung cancer with 40,470 breast cancer deaths predicted in 2009 [1]. Moreover, it has been estimated that as many as 10 million postmenopausal women in the

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Conflicts of interest statement
None declared.

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US are at increased risk for breast cancer [2]. The most important risk factor for breast cancer is age [3]. The incidence and mortality of breast cancer are particularly high in postmenopausal women, with 78% of all breast cancers occurring in women of more than 50 years of age and 86% of breast cancer deaths occurring in this age group [4]. Established risk factors for breast cancer explain only about 13% of breast cancer incidence among women in the US [5]. Thus, the causes of most cases of breast cancer remain unknown. Other possible etiologic factors that have also emerged from epidemiologic studies include:

Geographic variation

There are striking variations in breast cancer incidence rates. Breast cancer rates are higher in North America, northern Europe, and lowest in Asia [6]. We hypothesize that a high serum Ca:Mg ratio explains the discrepancies in the post-menopausal breast cancer incidence rates. An imbalance of the Ca/Mg intake may also lead to irregularities in many biological activities, such as DNA repair, cell proliferation, differentiation, and carcinogenesis [7]. For example, the ratio of Ca/Mg intake is significantly higher in the US population (2.8) than in the East Asian population (1.6) [8]. For example, Ca intake was significantly lower in Asian than US women, especially among the Chinese (only 256 ± 150 vs. 699 ± 313) [9].

Our preliminary data from medical charts review showed that the ratio serum calcium to serum magnesium was higher in post-menopausal breast cancer women ($n = 13$) than in postmenopausal women without cancer ($n = 6$) (4.91 ± 0.71 vs. 4.43 ± 0.44, respectively).

Race/ethnicity

There are also interracial differences. The highest rates, per 100,000 women, occur in whites (133 cases). The rates are lower in African Americans (118 cases), Asian Americans/ Pacific Islanders (89 cases), Hispanic/Latina women (89 cases), and American Indians/Alaska Natives (70 cases) [10]. Much of these ethnic differences are attributable to factors associated with lifestyle and biological factors [11]. For example, Plawecki et al. [12] showed that regardless of dietary assessment method used, white women had higher calcium intakes than black women. When using the calcium-focused food frequency questionnaire (CFFFQ), white women reported consuming approximately 43% more calcium than did black women (mean [SD] 1104 [632] mg for white women vs. 768 [531] mg for black women, $P < 0.001$). When using the 24-h recall method, mean calcium intake for white women was approximately 52% higher than intake for black women (875 [429] mg vs. 573 [365] mg, $P < 0.001$). Ford and Mokdad [13] found that the median intake of magnesium was 237 mg/day (mean 256 mg/day) among Caucasian women, 177 mg/day (mean 202 mg/day) among African American women, and 221 mg/day (mean 242 mg/day) among Mexican American women.

Obesity

Excess weight, particularly weight gain in adult life, is also related to a higher risk of postmenopausal breast cancer [14]. It has been shown that Mg deficit and obesity may independently lead to a higher risk for insulin resistance and cardiovascular disease [15]. Farhanghi et al. [16] found that serum magnesium levels in obese women were lower than non-obese women.

Alcohol

The only well-established individual diet-related risk factor for breast cancer other than obesity is alcohol consumption [17]. Acute and chronic alcoholism are the most common settings for hypomagnesemia [18]. Interestingly, alcohol abstention is more prevalent among

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blacks than whites, as well as being more prevalent among women than men. Almost 80% of black women abstain compared to 64% of white women [19].

Finally, heart disease, diabetes, hypertension, and stroke are moderately associated with increased risk for postmenopausal breast cancer [20–22]. Overall, the possible epidemiological factors point towards the role of specific intake of nutrients in the diet. Before describing the significance of Mg and Ca in postmenopausal breast cancer, we briefly review dietary intake and causes of Mg deficiency in the US population.

Dietary sources of magnesium

Food sources rich in Mg that are commonly consumed in the US are green vegetables, legumes (mainly beans and peas), unrefined whole grains, nuts and seeds [23]. Meat, fruit and dairy products have only a moderate amount of Mg content, whereas refined foods are poor sources of Mg. The US Food Nutrition Board of the Institute of Medicine has established the Recommended Dietary Allowance (RDA) for adult females should have at least 320 mg/day of Mg [24]. The usual dietary Mg intake for women in the US, however, falls below this recommendation. According to the United States Department of Agriculture (USDA) [25], the mean Mg intake for females is 228 mg/day (68% of the RDA). This deficiency in Mg intake is present from adolescence to old age. For example, the mean Mg intake for ages 31–50, is 236 mg/day (RDA: 320 mg); for ages 51–70, 239 mg/day (RDA: 320 mg). Ten percent of elderly women in the US consume less than 136 mg/day of Mg (<43% of RDA). Using the National Health and Nutrition Examination Survey, Moshfegh et al. [26] reported the estimated daily Mg intakes of 5% of women are: 138 mg/day (aged 51–70 years) and 126 mg/day (aged 71+ years).

Physiological role of magnesium

Mg is the fourth most abundant cation in the body and the second most prevalent intracellular cation [27]. Mg plays an essential role in more than 300 biological activities [28]. Within the cell, Mg affects the function of organelles such as sarcoplasmic reticulum, primarily by its ability to alter Ca influx [29,30] or mitochondria by altering their membrane's permeability to protons, which leads to alterations in the coupling of oxidative phosphorylation and electron transport chains, thus affecting the efficiency of ATP production. A decrease in serum Mg could decrease Mg levels inside the cells, which will lead to a decrease in Mg–ATP levels. The best recognized function of Mg is its association with ATP and the consequent facilitation of transphosphorylation reactions that are crucial to cell activation/deactivation as, for example, in signal transduction pathways. A decrease in Mg–ATP could increase cell proliferation by activating Ca channels (TRPM7) thereby leading to cancer [31]. TRPM7, a ubiquitously expressed ion channel, has a higher affinity for Mg than for Ca [32], and plays a central role in Mg homeostasis as well as in Mg uptake pathways [33]. Recently, the role of Mg in regulating cell proliferation was underscored by studies based on the deletion of the TRPM7, where Mg depletion causes growth arrest. In the following section, we will summarize the role of TRPM7 in the cell.

Causes of magnesium deficiency

The reduced intake of Mg may be due to an increased use of refined or processed cereals and carbohydrates from which the majority of Mg has been removed. The softening of "hard" water further removes variable quantities of Mg and may also contribute to reduced intake of Mg [34]. Mg deficiency is often caused by chronic alcoholism and gastrointestinal disorders [35]. Most frequently, hypomagnesemia is an acquired disorder; only in rare instances does hypomagnesemia have an underlying hereditary etiology [36]. Morbid conditions producing body Mg loss such as diabetes, alcoholism, malabsorption, and

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medications (diuretics, cyclosporine, aminoglycosides, cisplatin, amphotericin B) also exacerbate the problem [37]. On average, about one-third of the dietary Mg is eliminated in the urine. In addition, Mg loss also occurs through perspiration and as much as 10–15% of the total output of Mg can be recovered in the sweat [38]. Finally, this substantial dietary Mg deficit is particularly important in older women where gastrointestinal and renal mechanisms for Mg conservation may be less efficient than in younger women [39]. Mg depletion is frequently attributed to deregulation of factors controlling Mg metabolism and the reduction in the Mg exchange pools. Finally, Ca supplementation may accentuate the problem of reduced Mg levels by impairing the retention of Mg [40].

Impact of magnesium deficiency on calcium retention

In humans, studies on postmenopausal women have suggested that a sub-clinical dietary Mg deficiency (approximately 115 mg/day) compared to an adequate intake 330 mg/day of Mg increased Ca retention [41] and not by affecting its absorption from the gastrointestinal tract or regulation at the kidney level. Therefore, once the Ca concentration is high, Mg absorption could be significantly depressed. A decrease in serum Mg could decrease Mg levels inside the cells, which will lead to a decrease in Mg–ATP levels. This leads to an increase in Ca influx, which will increase Ca–ATP levels in the cells. An increase in Ca–ATP levels along with an increase in Ca influx could inappropriately activate Ca dependent cell proliferation thereby leading to cancer.

Transient receptor potential melastatin 7

TRPM7 [42], a widely expressed member of the TRPM family of ion channels [43] is a cation channel that is regulated by intracellular levels of Mg–ATP and is strongly activated when Mg–ATP falls below 1 mM. Furthermore, TRPM7 is permeable to both of the dominant divalent cations Ca and Mg. At physiological concentrations of extracellular Ca and Mg, activation of MagNuM (by decrease in Mg–ATP) allows significant Ca entry, but not Mg in cells [44]. Thus, TRPM7 can drive significant changes in intracellular Ca particularly after depletion of intracellular Mg–ATP. As a result this increase in cytosolic Ca leads to increased cell proliferation [31]. Elimination of TRPM7 by siRNA silencing markedly reduced the magnitude of spontaneous Ca influx, which decreased cell proliferation, and retarded G(1)/S cell cycle progression. As a result, the levels of Ca and Mg cations might become unbalanced in breast cancer patients. Furthermore, high intracellular concentrations of Mg suppress TRPM7 [45]. Overall this indicates that TRPM7 couples channel activity with the metabolic state of the cell, which highlights the importance of this channel in breast cancer.

Biological plausibility of magnesium and calcium

The increase of Mg influx in G1 is consistent with the modulation of cell cycle regulatory proteins (cyclin D1, Cdk4, p21cip1, p27kip1), as suggested by studies carried out in high or low Mg conditions [46] and on the need of high Mg availability during protein synthesis [47]. Moreover, Mg has a role in intracellular transphosphorylation reactions, which are critical for reactions that are associated with initiation of DNA synthesis and multiplication in cultured cells [48]. Ca, on the other hand, has been suggested as a short term regulator of cell growth and function, largely on the basis of its tightly regulated low cytoplasmic concentration [49]. Importantly, McKeehan and Ham [50] showed that (1) Ca and Mg have equally important roles in regulation of cellular multiplication that go beyond support of attachment and survival of non-proliferating cells; (2) transformation causes a selective loss of the regulatory role of Mg, but not Ca, in cellular multiplication; (3) in normal cells, Mg has its regulatory effect on a process more proximal to the intracellular events of cellular

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replication than those processes affected directly by Ca; (4) in normal, but not transformed cells, the regulatory effect of Ca is primarily mediated through Mg-dependent processes; (5) the role of Ca is more proximal than that of Mg to the action of regulatory macromolecules from serum in the chain of events which ultimately determine multiplication rate of normal cells. Intracellular Mg can modulate Ca signaling [51]. It has been shown that Mg is only elevated in cells with high Ca [52]. Nasser et al. [53] found a positive correlation between Mg–ATPase activity and Ca–ATPase. They concluded that decreased Mg–ATPase activity may contribute to increased intracellular Ca.

Why postmenopausal breast cancer?

Dietary intake of Mg in the US is less than the recommended amount. Furthermore, this dietary Mg deficit is pronounced in individuals older than 51 years of age where gastrointestinal and renal mechanisms for Mg conservation are less efficient than in younger populations. The National Institutes of Health also recommends 1000 mg/day of Ca for postmenopausal women younger than 65 years who take estrogen and 1500 mg/day for those who do not take estrogen to prevent osteoporosis. Although, the average dietary Ca intake for postmenopausal women in the US is approximately 600 mg/day, consumption of large quantities of Ca (e.g., via Ca supplements, self-medication such as calcium-containing antacids) can elevate serum Ca significantly. Finally, Mg intake decreased with increasing age (P for linear trend = 0.035 for Caucasians; P for linear trend < 0.001 for African Americans and Mexican Americans) [13].

Magnesium deficiency and postmenopausal breast cancer

In 1992, Sartori et al. [54] compared control subjects to patients diagnosed with breast cancer and showed that in cancer patients, serum Mg was significantly lower than in controls. Studies [55] have also reported that moderate alcohol intake increases breast cancer risk by approximately 7% per alcoholic drink per day. We speculate that alcohol may act by exacerbating Mg deficiency. Furthermore, alcohol consumption is known to deplete Mg, and Mg is one of the first supplements given to alcoholics when they stop and attempt to detoxify their body. Interestingly, alcohol consumption is the only dietary intake that has shown consistent and significant positive associations with breast cancer risk. The recent Million Women cohort study [56] reported that increasing alcohol consumption was associated with increased risk of breast cancer (12%, 95% CI: 9–14%, P-trend < 0.001), during an average 7.2 years of follow-up. Total and ionic magnesium serum concentrations are strongly correlated, and either gives an accurate assessment of magnesium status in health, irrespective of ethnicity [57].

Calcium level and postmenopausal breast cancer

The few observational studies reporting on serum Ca and post-menopausal breast cancer risk remain controversial, with some studies reporting a higher risk [58,59] and others no association [60] with high serum Ca levels. We believe this is because the key variable not considered is the Mg level in the same individuals, which influences TRPM7 function that will affect Ca influx and Ca–ATP levels. A decrease in Mg levels could activate TRPM7, which increases intracellular Ca levels, along with a decrease in Mg–ATP. This overall change in ATP and Ca levels could inappropriately activate Ca dependent cell proliferation thereby leading to cancer.

Thus, prospective epidemiological studies are urgently needed to assess levels of serum magnesium, serum calcium, TRPM7, and Mg–ATP levels in breast tissues/cells in relation to breast cancer risk and recurrence. Moreover, physiological experiments in breast tissues (monitoring Ca and Mg levels [61,62]) are also needed, along with detailed characterization

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with regard to the expression and function of TRPM7 in breast cancer. These results will be critical in understanding the onset/progression of breast cancer and could represent prospective drug targets for the development of the new generation of therapeutic approaches against breast cancer.

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