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Urinary magnesium and other elements in relation to mammographic breast density, a measure of breast cancer risk

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Abstract

Purpose: Heavy metals and other elements may act as breast carcinogens due to estrogenic activity. We investigated associations between urine concentrations of a panel of elements and breast density.

Methods: Mammographic density categories were abstracted from radiology reports of 725 women aged 40–65 years in the Avon Army of Women. A panel of 27 elements was quantified in urine using high resolution magnetic sector inductively coupled plasma mass spectroscopy. We applied LASSO (least absolute shrinkage and selection operator) logistic regression to the 27 elements and calculated odds ratios (OR) and 95% confidence intervals (CI) for dense versus non-dense breasts, adjusting for potential confounders.

Results: Of the 27 elements, only magnesium (Mg) was selected into the optimal regression model. The odds ratio for dense breasts associated with doubling the Mg concentration was 1.24 (95% CI 1.03–1.49). Doubling the calcium-to-magnesium ratio was inversely associated with dense breasts (OR 0.83, 95% CI 0.70–0.98).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Conclusions: Our cross-sectional study found that higher levels of urinary magnesium were associated with greater breast density. Prospective studies are needed to confirm whether magnesium as evaluated in urine is prospectively associated with breast density and, more importantly, breast cancer.

Keywords

Breast cancer; environmental metals; breast density; magnesium; LASSO

INTRODUCTION

Women whose mammograms show extremely dense breasts have approximately three-fold risk of invasive breast cancer compared to women with less dense breasts (1–3). The biological mechanism whereby breast density is related to increased breast cancer remains unclear, but breast density shares several risk factors with breast cancer, including use of hormone therapy, nulliparity, and older age at first birth (1,2). Additionally, magnesium, calcium, and other elements have been proposed as factors that can protect (4–6) or promote cancer (7–11) but their associations with breast density are uncertain (11).

Magnesium is obtained from the diet with higher doses arising from green vegetables, nuts and unprocessed cereals, and lower concentrations are seen in dairy products and processed foods (4,12,13). Previous studies suggest that dietary intake in the United States is lower than the estimated average requirement (14). Magnesium is required for many physiologic functions (5,12,13), including cell proliferation, signaling transduction (4), and DNA repair and synthesis (15). In cases of hypomagnesemia, higher levels of free radicals and inflammation may lead to DNA damage and mutations that can result in cancer (4,6), which highlights the significance of optimal concentrations of magnesium in intracellular and extracellular compartments. Previous studies have hypothesized an association between magnesium and breast cancer (16). However, few have investigated how magnesium and calcium – elements that are antagonistic in many physiologic functions (16, 17) – may be interconnected in their association with breast cancer.

The purpose of our study was to measure a panel of elements assessed in urine, including magnesium and calcium, and to describe associations of these elements with mammographic breast density, a marker of breast cancer risk.

METHODS

The University of Wisconsin Health Sciences Human Subjects Committee approved this study. Women were recruited online from the Dr. Susan Love Foundation Army of Women volunteers between December 2012 and May 2013 (18). Eligibility was limited to women aged 40–74 years without a personal history of breast cancer or breast reduction surgery or breast implants. Women were also required to report receiving a mammogram within the past 18 months. Of 1,500 women that completed the online eligibility survey, 1,004 women were eligible and received study materials; 790 women completed the study questionnaire and returned a signed consent form, spot urine sample, and recent mammography report to the study center. Of the mammography reports, 27 had no mention of breast density and 38

had ambiguous descriptions of density. Hence, 725 women had complete study information and were included in statistical analysis.

The study questionnaire elicited information regarding lifestyle factors that may influence exposure to metals and other elements including multivitamin intake, alcohol consumption, smoking history, reproductive and menstrual history, hormone medication use, and demographic factors. Breast Imaging-Reporting and Data System (BI-RADS) mammographic density categories were abstracted from radiology reports, defined as: a, almost entirely fatty; b, scattered fibroglandular density; c, heterogeneously dense; and d, extremely dense (19). Radiology reports were reviewed by a board-certified radiologist (E.S.B.), who adjudicated mammography reports that used density descriptors other than terminology recommended in the BI-RADS Atlas. BI-RADS classification has been widely used to describe breast density, has good reproducibility (20) and its association with breast cancer risk has been previously described (1).

Urine collection containers were sterile, acid-washed polypropylene bottles with screw top lids, a method previously used without evidence of contamination (10). A panel of 27 elements was quantified in urine using high resolution magnetic sector inductively coupled plasma mass spectroscopy including aluminum, antimony, arsenic, barium (Ba), beryllium, calcium (Ca), cadmium, cobalt, chromium, cesium (Cs), copper (Cu), iron (Fe), potassium (K), lithium (Li), magnesium (Mg), manganese (Mn), molybdenum, sodium (Na), nickel (Ni), phosphorus, lead, strontium (Sr), thallium, uranium, vanadium, tungsten, and zinc (21). This panel was assembled based on known or suspected associations with cancer and includes known carcinogens, metalloestrogens, which have been previously associated with hormone-driven cancers (22), and several redox active metals (Fe, Mn, Cu, Ni) which are capable of producing excess reactive oxygen species and subsequent inflammatory cascades. The alkaline earths (Ba, Sr) and alkali metals (Na, K, Li, Cs) are included (in addition to Ca and Mg) as they reflect major ion homeostasis in the body and several may compete for the same ion channels as the Ca and Mg. The panel also includes several elements present in multivitamin and multimineral supplements, whose associations with breast cancer remain unclear (23, 24).

Urinary element concentrations were normalized to urinary creatinine levels and log-transformed for statistical analysis. Least absolute shrinkage and selection operator (LASSO) logistic regression was used to identify urinary metals associated with dense breasts (BI-RADS category c or d) as compared with non-dense breasts (BI-RADS category a or b) (25). In addition to the 27 elements, potential confounders included in the model included age, alcohol consumption, parity, race/ethnicity, menopausal status, postmenopausal hormone use, body mass index, and census region.

LASSO is a variable selection and regularization method for regression models that enhances both prediction accuracy and interpretability of the model. LASSO creates a path of optimal coefficients starting from the null model with no active covariates to a saturated model with all covariates included and unpenalized. The LASSO penalty (the sum of the absolute values of the coefficients) results in a sequence of optimal solutions with some covariates with coefficients set to zero (variable selection). The optimal LASSO solution

was chosen to minimize the logistic regression deviance estimated using 10-fold cross-validation. The LASSO procedure is often described as a more democratic version of traditional forward stepwise regression, and the cross-validation procedure accounts for potential overfitting, indirectly accounting for multiple testing issues. The LASSO penalty was only applied to the 27 metals; the potential confounders were included without penalty in all models. Analyses were performed using the glmnet package in R version 3.2.3 (26).

RESULTS

Most of the women had dense breasts, BI-RADS c and d (65%). Women with non-dense breasts, BI-RADS a and b (35%), were more likely to be older, postmenopausal, and have greater body mass index compared to women with dense breasts BI-RADS c and d (Table 1).

Mean values of the 27 elements according to breast density are shown in Table 2. In age-adjusted models, a doubling in the concentration of magnesium was associated with increased odds ratios of dense breasts (OR 1.36, 95% CI 1.16–1.59). Confidence intervals for all of the remaining elements included the null value.

Of the 27 elements considered, only magnesium was selected as contributing to the optimal LASSO regression model (Figure). The last three elements to be dropped during automated variable selection—before the optimal model contained only magnesium—included beryllium, molybdenum, and nickel.

A doubling in the concentration of magnesium was associated with a 1.24 odds ratio (95% CI 1.03 – 1.49) of dense breasts. After additional adjustment for the concentration of calcium, a doubling in the concentration of magnesium was associated with a 1.32 odds ratio (95% CI 1.06 – 1.65) of dense breasts. A doubling in the ratio of Ca:Mg was associated with a 0.83 odds ratio (95% CI 0.70–0.98) of dense breasts.

DISCUSSION

Our results suggest a positive association between urine magnesium and dense breasts, and an inverse association with the Ca:Mg ratio, among healthy volunteers. To our knowledge this is the first report of these associations. Our confidence in the study results is supported by the large sample size, objective measure of the elements in urine, and statistical approach that permitted the single and joint contributions of each element.

Epidemiologic studies suggest that high levels of magnesium intake are associated with a lower incidence of esophageal and liver cancer (27–29), and decreased mortality due to colon, breast, prostate and ovarian cancers (7). Ma et al evaluated the dietary intake of magnesium among Japanese men and women, and concluded that higher dietary intake of magnesium decreased risk of colorectal cancer in men, but not in women (30). In our study, doubling of magnesium is associated with greater breast density, which could be a reflection of estradiol effects on breast tissue, magnesium reabsorption, and subsequent effects of the latter on normal cell proliferation (13). Higher mammographic density might be a result of increased epithelium and stroma proliferation (31).

Our results also suggest that a doubling in the Ca:Mg ratio was associated with lower mammographic breast density. Greater breast density is strongly associated with all breast cancer subtypes, but especially with larger tumor sizes, positive lymph nodes, and estrogen receptor-negative status.(32) These results are consistent with a published breast cancer study that showed that postmenopausal women with a higher Ca:Mg ratio had longer survival (16), possibly due to less aggressive features, lower recurrence and lower risk of a second primary (3). Using a prospective cohort of patients in Western New York State, Tao et al described improved overall survival among breast cancer patients that had higher magnesium dietary intake, and the association was stronger among those with high Ca:Mg ratio (16). However, Sahmoun et al hypothesized that a high Ca:Mg ratio is associated with increased cancer risk due to cell proliferation mediated by calcium (8), which was partially demonstrated by Sun et al using prostate cancer cells (9).

Magnesium homeostasis is mostly dependent on renal absorption, via active reabsorption mediated by transient receptor potential melastatin 6 (TRPM-6), and with minimal variations due to dietary intake (13). Reabsorption follows a circadian rhythm with maximal excretion at night (33) and further modulation is performed by estrogen, progesterone, testosterone, and epidermal growth factor (34,35). In vitro, 17 β -estradiol has been associated with increased magnesium serum levels (34,36) which correlate with higher magnesium excretion among healthy menopausal women (37,38). In human studies, estrogen peaks at the time of ovulation are associated with low levels of ionized magnesium (38), elevated ionized calcium, and elevated Ca:Mg ratio; these effects might be caused by an intracellular shift of magnesium, due to unknown mechanisms (39).

Magnesium metabolism is altered in cancer cells (4,5,9) they contain higher intracellular concentration of magnesium than normal cells (7,5), and their growth is not inhibited by magnesium restriction (4,7), these adaptations provide metabolic advantages: resistance to senescence and apoptosis (40) inhibition of p53 tumor suppressor gene (41), and inhibition of DNA repair with altered response to normal growth signals (7).

A strength of our study is that by using healthy volunteers, we avoid confounding by magnesium metabolism changes and any other magnesium abnormalities observed in cancer patients (4,39). However, these healthy volunteers were, in general, highly educated and overwhelmingly of European ancestry. A more diverse sample may provide greater variation in exposure levels to the 27 elements, including magnesium, which would facilitate evaluation of the relation between more extreme exposure values and breast density. In addition, our method of evaluation of magnesium levels was restricted to urine, and some individuals may have normal urine levels while intracellular magnesium is depleted (12,13). For these patients, a load test of magnesium or measurement of 24-hour urinary magnesium may more accurately reflect the intracellular status (21). While evidence suggests that urinary concentrations may be a fair measure of systemic load, more information is needed about the correlations between a one-time sample and 24 hour-collection, especially considering the circadian rhythm of magnesium excretion.

CONCLUSIONS

Our cross-sectional study suggests that higher levels of urine magnesium are associated with greater breast density; a doubling of the Ca:Mg ratio was inversely associated with density. Future studies are warranted to evaluate whether urine magnesium is prospectively associated with breast cancer risk.

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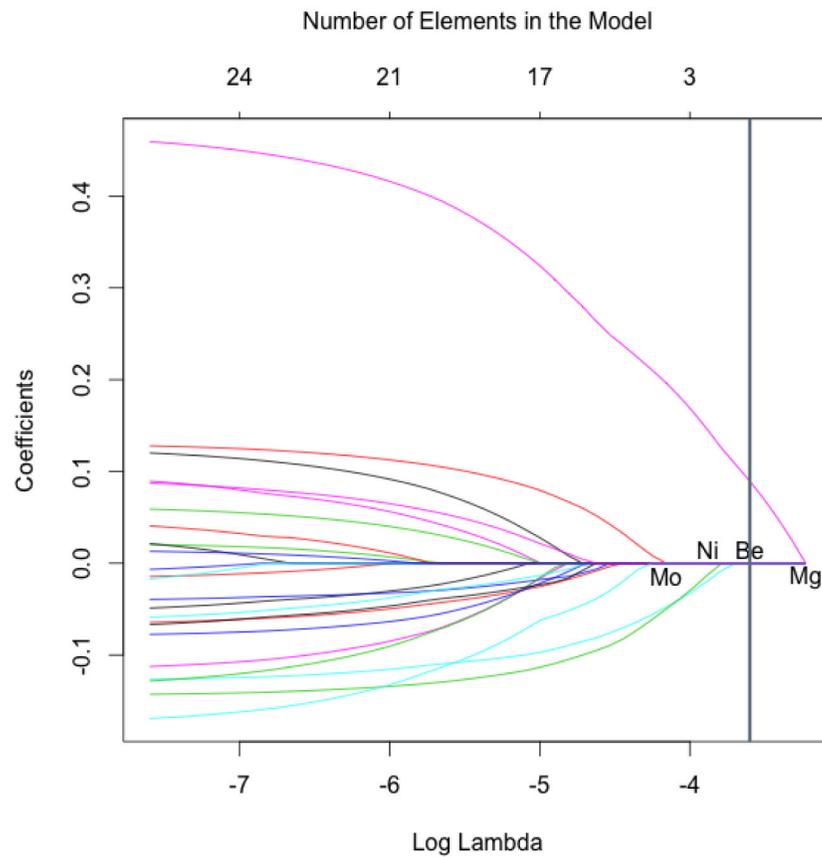
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**Figure.**

Automated variable selection for a regression model of heavy metals and other elements in relation to breast density. Logistic regression coefficients for each element and the number of elements in the regression model shown as a function of the LASSO penalty parameter (log lambda). The model on the far left corresponds to the unconstrained maximum likelihood estimate (all elements); the model on the far right corresponds to the null model (no elements). The vertical line corresponds to the optimal model by cross-validation with a single element, magnesium. Every model includes all potential confounders. Abbreviations: LASSO, least absolute shrinkage and selection operator; Be, beryllium; Mg, magnesium; Mo, molybdenum; Ni, nickel

Table 1:

Selected characteristics of participating women according to mammographically measured breast density, Avon Army of Women, 2014

	Non-dense breasts ^a N=252 %	Dense breasts ^b N=473 %
Age (yr)		
40-45	10	14
46-50	15	21
51-55	19	23
56-60	20	20
61-65	36	22
Alcohol consumption		
Never	19	18
Light	44	47
Moderate	18	18
Heavy	19	18
Multivitamin supplement use		
No	44	44
Yes	56	56
Number of full-term pregnancies		
0	27	27
1	15	16
2	40	38
3	18	18
Ancestry		
European	96	95
Other	4	5
Postmenopausal hormone use^c		
Never	58	64
Former	28	20
Current	13	15
Menopausal status		
Premenopausal	23	37
Postmenopausal	77	61
Smoking history		
Never	65	69
Ever	34	31
Body mass index (kg/m²)		
<25	37	63
25-30	33	29
30	29	8

	Non-dense breasts ^a N=252 %	Dense breasts ^b N=473 %
Geographic region of residence		
Midwest	30	21
Northeast	22	26
South	29	32
West	19	22

^aDefined as BI-RADS *a* (almost entirely fatty) and *b* (scattered fibroglandular density).

^bDefined as BI-RADS *c* (heterogeneously dense) and *d* (extremely dense).

^cAmong postmenopausal women only.

Abbreviation: BI-RADS, Breast Imaging-Reporting and Data System.

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Table 2.

Univariate results of 27 heavy metals and elements in relation to mammographic density, Avon Army of Women, 2014

Element	Non-dense breasts ^a Mean concentration (N=252)	Dense breasts ^b Mean concentration (N=473)	Age-Adjusted Odds Ratio ^c (95% CI)
Aluminum	5.19	4.51	0.95 (0.82-1.11)
Antimony	0.0465	0.0456	1.01 (0.86-1.19)
Arsenic	25.26	29.35	1.06 (0.97-1.16)
Barium	2.12	2.48	1.04 (0.92-1.17)
Beryllium	0.2123	0.1978	0.98 (0.88-1.10)
Calcium	123,984.82	126,664.38	1.09 (0.95-1.25)
Cadmium	0.2786	0.2487	0.97 (0.85-1.10)
Cobalt	0.5076	0.5037	1.03 (0.91-1.18)
Chromium	0.4972	0.4077	1.01 (0.89-1.15)
Cesium	6.20	5.55	1.18 (0.91-1.52)
Copper	6.34	5.96	0.85 (0.61-1.19)
Iron	7.24	7.45	0.95 (0.82-1.11)
Potassium	2,211,816.82	2,038,089.28	1.12 (0.96-1.30)
Lithium	32.42	31.08	0.98 (0.83-1.17)
Magnesium	51406.73	58,669.73	1.36 (1.16-1.59)
Manganese	0.1602	0.1859	1.04 (0.92-1.19)
Molybdenum	48.06	48.96	1.03 (0.87-1.19)
Sodium	197,622.19	1,730,927.98	1.01 (0.90-1.14)
Nickel	1.9138	1.8585	1.00 (0.87-1.15)
Phosphorus	519,179.43	510,540.91	0.97 (0.79-1.19)
Lead	0.4483	0.4036	1.07 (0.89-1.29)
Strontium	146.43	236.25	1.12 (0.96-1.31)
Thallium	0.1894	0.1820	1.21 (0.97-1.47)
Uranium	0.01426	0.01561	1.06 (0.98-1.16)
Vanadium	0.1299	0.1808	0.93 (0.81-1.07)
Tungsten	0.5230	0.4058	0.98 (0.89-1.09)
Zinc	258.71	232.61	0.94 (0.80-1.10)

^aDefined as BI-RADS *a* (almost entirely fatty) and *b* (scattered fibroglandular density).

^bDefined as BI-RADS *c* (heterogeneously dense) and *d* (extremely dense).

^cEstimates the odds ratio for dense breasts associated with a doubling in the concentration of the elements, normalized for creatinine and adjusted for age.

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System; CI, confidence interval.