ARIC Manuscript Proposal #1831

PC Reviewed: 8/9/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum and dietary magnesium and cancer incidence in the ARIC study.

b. Abbreviated Title (Length 26 characters): Magnesium and cancer

2. Writing Group:
Writing group members: Anna Prizment, Pamela Lutsey, Kim Robien, Corinne Joshu, Aaron Folsom, other interested investigators

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AP___ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
Analyses will begin after the ARIC Committee approves the proposal. We anticipate the manuscript will be completed within 1 year.

4. Rationale:

Magnesium (Mg) is an essential mineral found in several dietary sources, including whole grains, green leafy vegetables, legumes, and nuts. Dietary Mg intakes for ~56% of adults in the United States are below the Estimated Average Requirement (EAR). Mg intakes below the EAR are especially prevalent among the poor, teenagers, the obese, African Americans, and the elderly (1).

Mg is important for maintaining the integrity of DNA. Mg cations bind to DNA and reduce the negative charge density, thereby stabilizing the structure of DNA (1). Mg is also an essential cofactor for several enzyme systems involving DNA repair such as nucleotide excision repair, base excision repair and mismatch repair (2). In primary human cells in vitro, magnesium deficiency "leads to accelerated telomere shortening, activation of cell-cycle arrest proteins, premature senescence, and mitochondrial DNA damage" (1). Other studies found that Mg plays a role in protection against oxidative stress and protection against inflammation (3, 4).

In humans, moderate Mg deficiency has been associated with age, hypertension, stroke, osteoporosis, diabetes, and the metabolic syndrome (1). Several epidemiological studies reported inverse associations of serum Mg with overall death (by 40%) and death from cancer (50%) (5). Case-control and cohort studies have also found inverse associations of dietary magnesium intake with colorectal (6,7,9,10) and lung (2) cancers. Additionally, serum Mg has also been inversely related to breast (11) and prostate cancers (12). Two studies also reported inverse associations of Mg/Ca (calcium) ratio with colorectal adenoma and prostate cancers (for dietary and serum Mg, respectively) (6, 12), since Ca and Mg levels in the body are jointly regulated through a negative feedback system, and through competition for intestinal absorption and renal reabsorption (6, 12, 13).

Thus, only few studies examined associations of Mg with prostate, lung, and breast cancer, and all of them were case-control studies. Although several studies investigated associations between Mg and colorectal cancer in case-control and cohort studies, all but one of them examined only dietary intake, which usually doesn't account for Mg from drinking water. Thus, our goal is to conduct a comprehensive analysis by investigating the association of serum and dietary Mg with cancer incidence (total, breast, colorectal, prostate, and lung), as well as the associations of Mg/Ca ratio with these outcomes**.**

5. Main Hypothesis/Study Questions:

- Examine associations of serum Mg and dietary Mg intake with the risk of total and specific cancers: breast, colorectal, prostate, lung cancers after adjusting for serum Ca and Ca intake, respectively.
- Evaluate whether BMI and smoking modify each of the associations between Mg and cancer
- If power allows, examine whether or not the CRP at Visit 4 modifies association of Mg with cancer.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Prospective cohort study

Inclusion/Exclusion: *inclusion*: all ARIC visit 1 participants free of cancer; *exclusion*: those who did not give consent to participate in cancer studies, participants with missing serum Mg and dietary Mg data at Visit 1 in the relevant analyses. In the dietary analysis, only those with extreme caloric intakes or low-quality dietary data.

Independent variables: Magnesium from diet and serum
Dietary Mg intake (from Visit 1 and Visit 3) was computed by multiplying the Mg content of the specified serving of each food item by the frequency of its daily consumption and summing over all items.
Serum Mg was measured at Visit 1 and Visit 2.

Dependent Variable: Overall and site-specific cancer incidence through 2006.

Other variables of interest: age, race, sex, study site, education, BMI, WHR, smoking status, pack-years of smoking, alcohol consumption, physical activity, diabetes, kidney disease, white blood cell count, fibrinogen, use of diuretics, use of other antihypertensive meds, serum calcium, potassium, creatinine , HDL, LDL, total energy, dietary potassium, calcium, fiber, protein, caffeine, and polyunsaturated to saturated fat ratio. Use of post-menopausal hormones (current/former/never use), parity and age at first birth for women.

Analysis plan: We will use a proportional hazards model to estimate the multivariate adjusted risk of each cancer in relation to dietary and serum Mg. Serum and dietary Mg will be modeled as quartiles and as continuous variables.
We will use average Mg dietary intake for those people who participated at Visit 1 and Visit 3 and were censored after Visit 3 (Visit 1 and Visit 2 data will be used for the analysis of serum Mg). If people were censored before Visit 3 or did not have Mg data for Visit 3 (Visit 2 for serum Mg), data for Mg at Visit 1 will be used. Follow-up will start at Visit 1 for all the participants.

The following models will be used to analyze the associations of Ma with cancers:
Model 1: adjusted for age, gender, race, and ARIC study site

Model 2a for serum Mg: Model 1 additionally adjusted for BMI, smoking status, pack-years of smoking, drinking status, education level, diabetes, kidney disease, use of diuretics and other antihypertensive meds, as well as HDL-c, LDL-c, serum calcium, potassium, serum creatinine, and markers of inflammation (i.e., fibrinogen, white blood cell count, and, in additional analysis, CRP at visit 4)

Model 2b for dietary Mg: Model 1 additionally adjusted for BMI, smoking status, pack-years of smoking, drinking status, education level, diabetes, kidney disease, use of diuretics and other antihypertensive meds, as well as total energy intake, dietary calcium, potassium, fiber, protein, caffeine, and polyunsaturated to saturated fat ratio.

For women, use of post-menopausal hormones (current/former/never use) will be also considered as an additional confounder in Model 2 (a and b), as well as parity and age at first birth in the breast cancer analysis.

7.a. Will the data be used for non-CVD analysis in this manuscript?
__x__ Yes ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
__x__ Yes ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
____ Yes _ x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____Yes ____No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___x___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal

_x__ A. primarily the result of an ancillary study (list number* _1995.04__)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

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