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Genetically predicted circulating concentrations of micro-nutrients and risk of breast cancer: A Mendelian randomization study

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Short title

Micronutrients and breast cancer risk: An MR study

Key words: Mendelian randomization, diet, nutrition, breast cancer, causal inference

Abbreviations

BCAC, Breast Cancer Association Consortium; CaSR, calcium-sensing receptor; CI, confidence interval; EAF, effect allele frequency; ER, estrogen receptor; FFQ, food frequency questionnaires; GWAS, Genome-Wide Association Studies; HR, hazard ratio; IgE, immunoglobulin E; IVW, inverse variance weighted; LD, linkage disequilibrium; MR-PRESSO, MR pleiotropy residual sum and outlier test; OR, odds ratio; MAF, minor allele frequency; MR, mendelian randomization; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation; SE, standard error; SNP, single nucleotide polymorphisms; WCRF, World Cancer Research Fund

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Novelty & Impact: The literature of circulating concentrations of minerals and vitamins with risk of breast cancer is generally limited and evidence from clinical trials is also lacking. We conducted a Mendelian randomization study to investigate whether genetically predicted concentrations of 11 micro-nutrients are associated with risk of breast cancer. An increased risk of overall and oestrogen-receptor positive disease was observed for genetically predicted higher concentrations of magnesium.

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Abstract

The epidemiological literature reports inconsistent associations between consumption or circulating concentrations of micro-nutrients and breast cancer risk. We investigated associations between genetically predicted concentrations of 11 micro-nutrients (beta-carotene, calcium, copper, folate, iron, magnesium, phosphorus, selenium, vitamin B6, vitamin B12 and zinc) and breast cancer risk using Mendelian randomization (MR). A two-sample MR study was conducted using 122,977 women with breast cancer and 105,974 controls from the Breast Cancer Association Consortium. MR analyses were conducted using the inverse variance weighted approach, and sensitivity analyses were conducted to assess the impact of potential violations of MR assumptions. One standard deviation (SD: 0.08 mmol/L) higher genetically predicted concentration of magnesium was associated with a 17% (odds ratio [OR]: 1.17, 95% confidence interval [CI]: 1.10 to 1.25, P-value=9.1×10^{-7}) and 20% (OR: 1.20, 95% CI: 1.08 to 1.34, P-value=3.2×10^{-6}) higher risk of overall and ER^{+ve} breast cancer, respectively. An inverse association was observed for a SD (0.5 mg/dL) higher genetically predicted phosphorus concentration and ER^{-ve} breast cancer (OR: 0.84, 95% CI: 0.72 to 0.98, P-value=0.03). There was little evidence that any other nutrient was associated with breast cancer. The results for magnesium were robust under all sensitivity analyses and survived correction for multiple comparisons. Higher circulating concentrations of magnesium and potentially phosphorus may affect breast cancer risk. Further work is required to replicate these findings and investigate underlying mechanisms.

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Introduction

Breast cancer is the most common cancer in women with an estimated 2.1 million new cases and over half a million deaths worldwide in 2018 [1]. Breast cancer is a heterogeneous disease and its epidemiology varies with menopausal and tumour receptor status at time of diagnosis. Established risk factors for post-menopausal breast cancer include adiposity, endogenous concentrations of estrogens and androgens and reproductive factors such as early menarche, late menopause, late age at first pregnancy and hormone replacement therapy [2]. The role of nutrition in breast cancer development is unclear. The World Cancer Research Fund (WCRF) has recently systematically reviewed all literature on the associations of dietary and nutritional factors with breast cancer [3]. The WCRF report concluded that the evidence was strong only for a positive association between alcohol consumption and risk of pre- and post-menopausal breast cancer, whereas limited but suggestive evidence was found for inverse associations between consumption of non-starchy vegetables and foods containing carotenoids and calcium with risk of pre- and post-menopausal breast cancer [3]. The literature on circulating concentrations of minerals and vitamins with risk of breast cancer is generally not extensive with perhaps the exceptions of carotenoids and vitamin D [3].

Most of the evidence regarding the nutritional epidemiology of breast cancer comes from observational studies that often rely on food frequency questionnaires (FFQ) to measure the consumption of foods and nutrients. This approach is prone to measurement error, because it is based on participants' self-reports that might be inaccurate leading to biased results [4]. Furthermore, individuals who follow different dietary patterns might also differ in other aspects, which are not always adequately controlled for in statistical confounder adjustments [5, 6]. Evidence from clinical trials is

also lacking, as there are not many adequately powered trials that have evaluated the effect of micro-nutrients and cancer risk [7-12].

A Mendelian randomization (MR) approach can be used to assess the existence of a potential causal association between a risk factor and disease by using genetic variants as instrumental variables for the risk factor of interest [13]. As genotype is allocated randomly at conception, genetic variants are not influenced by potential confounding factors, such as environmental exposures, and cannot be altered by disease occurrence.

The aim of the current study was to investigate potential causal associations of genetically predicted circulating concentrations of minerals and vitamins with risk of overall breast cancer and cancer by estrogen receptor status (ER^{+ve} and ER^{-ve}) using MR methodology.

Materials and Methods

Data on the genetic epidemiology of circulating nutrients concentrations

The Genome-Wide Association Studies (GWAS) catalog (https://www.ebi.ac.uk/gwas) and Pubmed (https://www.ncbi.nlm.nih.gov/pubmed) were searched (last checked on October 2019) for published GWASs on circulating concentrations of minerals and vitamins that were conducted in populations of European ancestry. The initial list included 20 nutrients: beta-carotene, calcium, copper, folate, iron, magnesium, phosphorus, potassium, retinol, selenium, sodium, zinc and vitamins B1, B2, B6, B12, C, D, E, and K, for which associations for breast have been reported in the literature [3]. Vitamin D was excluded because recent MR studies have investigated the role of circulating vitamin D concentrations and risk of

breast cancer [14, 15]. Potassium, sodium, vitamins B1, B2, C and K were also excluded because either no genome-wide significant results have been reported [16, 17] or no GWAS has been conducted. Two further GWAS, those for circulating vitamin E and retinol, were excluded because they adjusted for body mass index (BMI), which may bias MR estimates [18-21]. Published GWAS for 11 nutrients were finally retrieved, namely beta-carotene, calcium, copper, folate, iron, magnesium, phosphorus, selenium, vitamins B6 and B12, and zinc [16, 22-30]. In the case of calcium, apart from the already published GWAS study[23] a more recent one that has been conducted in UK Biobank and published on a pre-print server was also used [24]. Single nucleotide polymorphisms (SNPs) that independently affected the concentrations of these nutrients at a genome wide significance level ($p < 5 \times 10^{-8}$) and were not in linkage disequilibrium (LD $r^2 \leq 0.1$) were obtained. For serum iron, we used summary estimates for three (rs1800562, rs1799945 and rs855791) out of the five (rs1800562, rs1799945 and rs855791, rs7385804, rs8177240) available genome-wide significant SNPs, because these SNPs showed a concordant effect on serum iron, ferritin, transferrin and transferrin saturation, and have been associated with an overall increased systemic iron status [29, 31, 32]. Three additional SNPs with minor allele frequency (MAF) smaller than 5% (rs12272669, rs2336573, rs6859667) in the initial GWAS papers for selenium and vitamin B12 were excluded from the final list of SNPs since their effects might be unstable due to their small MAF [27, 28]. In total, summary association data for 259 common (minor allele frequency ≥ 0.05) genetic variants associated with the 11 nutrients of interest was obtained. Detailed information on the selected genetic variants is provided on Supplementary Table 1.

Data on the genetic epidemiology of breast cancer

The genetic effects of the selected instruments on risk of overall breast cancer and cancer by estrogen receptor status were obtained from a recently published large GWAS of almost 230,000 participants (122,977 breast cancer cases [69,501 ER^{+ve}, 21,468 ER^{-ve}] and 105,974 controls) of European ancestry from the Breast Cancer Association Consortium (BCAC). Genotypes were imputed using either SHAPEIT2 and IMPUTE or MACH and Minimac and the regression models were adjusted for the first ten principal components in order to adjust for population stratification and country or study. [33]. The summary data are available on the consortium's website (http://bcac.ccge.medschl.cam.ac.uk/). Out of the 259 SNPs, rs778805, that was associated with vitamin B12, was significantly associated with risk of overall breast cancer, and rs4072037, that was associated with magnesium, was significantly associated with both overall and ER^{+ve} breast cancer (Supplementary Table 1). The primary and secondary endpoints of this study did not change during the conduct of the analyses or after the analyses.

Statistical power

Power calculations were performed using an online tool available at http://cnsgenomics.com/shiny/mRnd/ [34]. The statistical power to capture an OR of 1.10 per a standard deviation (SD) change in the circulating concentrations of the nutrients, given a sample size of 228,951 participants, type 1 error of 5% and a proportion of cases equal to 0.54, ranged from 0.55 for calcium to 1 for calcium using the UK Biobank GWAS study, copper, vitamin B12 and zinc, and the statistical power was between 0.80 and 1 for another four micro-nutrients (i.e., beta-carotene, iron, magnesium, selenium) (Table 1).

Mendelian Randomization analysis

Two-sample MR using summary association data was performed. In the case of beta-carotene, where only one SNP was available, the effect estimate was calculated as the ratio of the SNP-outcome over the SNP-nutrient association [35], whereas the fixed – effect inverse variance weighted (IVW) method was implemented when the instruments consisted of multiple SNPs, and this analysis can be thought as a meta-analysis of single SNP effects [35, 36]. The beta estimates from the regressions for circulating concentrations for beta-carotene, copper, selenium, vitamin B6, and zinc were transformed from the logarithmic scale that were originally reported in the published GWAS to the natural scale using a published formula [37]. All reported associations correspond to OR for risk of breast cancer per SD change in the circulating concentrations of the nutrients. We applied a Bonferroni-type correction for multiple comparisons based on the number of investigated micro-nutrients (P=0.05/11=0.0045).

To be valid instruments for the MR analysis, the selected genetic variants must meet the following criteria: i) be associated with the circulating concentrations of the nutrients, ii) be independent of any potential confounding variable of the nutrient – breast cancer association, and iii) affect breast cancer only through the nutrient being instrumented and not via any other pathway [38]. The strength of each instrument was measured using the F statistic calculated by the formula: $F = R^2(N-2)/(1-R^2)$, where R^2 is the proportion of the explained variance of the nutrient by the genetic instrument and *N* the sample size of the GWAS for the SNP-nutrient association [39]. The R^2 was calculated using an already published formula [40].

Sensitivity analyses

Statistical analyses were performed to examine the robustness of the MR results against potential violation of the second and third MR assumptions. We evaluated whether the selected genetic instruments were associated with secondary phenotypes in Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/) and GWAS catalog [41, 42]. To further check for existence of horizontal pleiotropy (violating the third MR assumption), we computed the Cochran's Q statistic, which quantifies the extent to which any differences in the individual effect sizes among the selected genetic variants is due to real differences between SNPs rather than sampling error [43]. When there was evidence of such heterogeneity, we assessed also a random effects IVW MR analysis [44]. We also assessed potential presence of horizontal pleiotropy using MR-Egger regression. This provides a statistical test for horizontal pleiotropy based on its intercept term, when it is different from zero. [45]. The slope of the MR-Egger regression, as well as, estimates from the weighted median and the weighted mode approach (WMA) provide valid MR estimates under the presence of horizontal pleiotropy [38, 45, 46]. Specifically, the weighted median approach provides a valid MR estimate when up to 50% of the included instruments are invalid to the 2nd and 3rd MR assumptions, whereas the estimate from the weighted mode is valid when the plurality of the genetic variants are valid instruments [38, 46]. The MR pleiotropy residual sum and outlier test (MR-PRESSO) was also implemented to identify outlying genetic variants and analyses were re-run after excluding these variants [47]. Finally, a leave one SNP out analysis was performed to examine the robustness of the MR estimates and whether any association was driven by any specific SNP. All analyses were implemented in the statistical software R version 3.4.3 using the package MendelianRandomization [48].

Results

Mendelian randomization estimates

A SD (0.08 mmol/L) higher genetically predicted concentration of magnesium was associated with a 17% (OR: 1.17, 95% CI: 1.10 to 1.22, $P=9.10\times10^{-7}$) and 20% (OR: 1.20, 95% CI: 1.11 to 1.30, $P=3.17\times10^{-6}$) higher risk of overall and ER^{+ve} breast cancer, respectively. An inverse association was observed for a SD (0.50 mg/dL) higher genetically predicted phosphorus concentration and risk of ER^{-ve} breast cancer (OR: 0.84, 95% CI: 0.72 to 0.98, $P=0.03$). A suggestive inverse association was observed for a SD (0.48 mg/dL) higher genetically predicted calcium concentration and risk of overall breast cancer (OR: 0.91, 95% CI: 0.83 to 1.00, $P=0.06$). However, no evidence for association with breast cancer was observed when the extended SNP instrument from UK Biobank was used (OR per SD: 0.97, 95% CI: 0.83 to 1.13, $P=0.68$). There was little evidence that any of the other nutrients were associated with risk of breast cancer or its subtypes (Figure 1). Only the results for magnesium survived correction for multiple comparisons.

Evaluation of Mendelian randomization assumptions

The F-statistic was larger than 10 for all the included variants implying absence of weak instruments (minimum value=16, maximum value=420) (Supplementary Table 1).

Cochran's Q test was not significant for all analyses, except for vitamin B12 and overall breast cancer risk (Cochran's Q $P= 0.02$) however, no change was observed in the results after performing the random effects IVW MR (Supplementary Table 2). Additionally, some indication of horizontal pleiotropy was found in the non UK Biobank analysis of calcium and overall breast cancer risk based on the MR-Egger test (intercept $P= 0.02$) (Supplementary Table 2).

The MR-Egger regression, the weighted median and the weighted mode methods confirmed the IVW per a SD higher genetically predicted magnesium concentrations for overall breast cancer ($OR_{MR-Egger}$=1.24, 95% CI: 1.01 to 1.53; $OR_{weighted\ median}$=1.20, 95% CI: 1.10 to 1.31, OR_{MBE}=1.21, 95% CI: 1.12 to 1.39) and ER^{+ve} breast cancer ($OR_{MR-Egger}$=1.44, 95% CI: 1.05 to 1.97; $OR_{weighted\ median}$=1.19, 95% CI: 1.05 to 1.34, $OR_{weighted\ mode}$=1.36, 95% CI: 1.16 to 1.59) (Supplementary Table 3). A positive association was observed between genetically predicted vitamin B12 concentrations and overall breast cancer risk based on the weighted median approach (OR: 1.08, 95% CI: 1.01 to 1.15). There was little evidence that any of the other nutrients were associated with risk of breast cancer in sensitivity analyses (Supplementary Table 3). Finally, the MR-PRESSO analysis did not reveal any outlying SNPs, which was also evident when we estimated and plotted the MR results for all nutrients by each separate SNP (Supplementary Figures 1-10).

When we iteratively excluded one SNP at a time from all genetic instruments to further probe into potential SNP outliers, the positive association between genetically predicted magnesium concentrations and risk of overall and ER^{+ve} breast cancer remained significant (Supplementary Table 4). However, when rs4072037 was removed from the genetic instrument for magnesium concentrations, the associations for risk of overall (OR: 1.11, 95% CL: 1.02 to 1.21) and ER^{+ve} breast cancer (OR: 1.09, 95% CL: 0.98 to 1.21) were slightly attenuated. There was little evidence that any of the other nutrients were associated with risk of breast cancer in the leave one out analysis with the exceptions described below. The inverse association observed in the IVW analysis between genetically predicted phosphorus concentration and the risk of ER^{-ve} breast cancer was not present after removal of rs1697421, rs947583 or rs297818. When rs1801725 was excluded from the 7SNP genetic instrument of

calcium concentrations, a protective effect was observed for overall (OR: 0.79, 95% CI: 0.68 to 0.91) and ER^{+ve} breast cancer (OR: 0.82, 95% CL: 0.69 to 0.98).

Several genome-wide significant associations of the genetic instruments with secondary traits were observed (Supplementary Table 5). Some of these may be associated with breast cancer and are potential causes of horizontal pleiotropy, namely associations with diabetes, height, insulin resistance, C-reactive protein, glycosylated haemoglobin, and age at menarche. However, when the SNPs that were associated with the latter secondary phenotypes were excluded in the leave one out analysis, the observed associations of the genetic instruments with breast cancer did not change (Supplementary Table 4).

Discussion

In this comprehensive MR analysis of 11 nutrient concentrations with risk of breast cancer, a positive association was observed for genetically elevated concentrations of circulating magnesium and risk of total and ER^{+ve} breast cancer, which was robust to sensitivity analyses and to correction for multiple comparisons. Potential inverse association of circulating phosphorus concentrations with ER^{-ve} breast cancer was observed in the main analysis, but were not robust to sensitivity analyses or multiplicity correction.

The literature on the association of dietary or circulating magnesium and the risk of breast cancer is scarce and inconclusive. Only one cohort study, involving 12,902 women aged 35-64 years at baseline with 415 breast cancers developed during a mean follow-up of 11 years, has reported on dietary magnesium in association with overall breast cancer risk. This study reported little evidence for an association (hazard ratio [HR]: 0.97, 95% CI: 0.69 to 1.35) comparing the 1^{st} to the 4^{th} quartile of

magnesium consumption [49]. In a cross-sectional study of 725 women, urinary magnesium levels were positively associated with breast density, although the interpretation of this finding is unclear, as breast density is a risk factor for breast cancer but it may also obscure detection of the disease [50-52]. The genetic instruments used in our analysis affect magnesium homeostasis and mechanistic studies suggest that increased concentrations of magnesium within breast cancer cells can lead to tumour progression through the regulation of enzymes involved in energy generation, and its presence is also needed for cell adhesion and cancer metastasis [53, 54]. Evidence from animal studies suggests that magnesium has a protective effect in the early phases of chemical carcinogenesis but promotes tumour growth [55]. There are no magnesium supplementation trials assessing relevant cancer outcomes. Our finding of a positive association between genetically predicted magnesium concentrations and risk of breast cancer should be further evaluated in humans and animals using observational and interventional designs.

An inverse association was observed in our analysis between concentrations of phosphorus and ER^{-ve} breast cancer. We found only one relevant cohort study involving 186,620 women, where 4,925 incident breast cancers developed during a mean follow-up of 13 years, reporting that a SD (0.17 mmol/L) increase in serum inorganic phosphate levels were inversely associated with total breast cancer risk (HR: 0.93, 95% CI: 0.90 to 0.96), but these estimates were not adjusted for potentially important confounders such as alcohol consumption and smoking status [56]. Our analysis did not confirm this association for total breast cancer (OR: 0.96, 95% CI: 0.88 to 1.04), but found an inverse association for ER^{-ve} disease (OR: 0.84, 95% CI: 0.72 to 0.98). Studies have linked estrogen levels with negative regulation of circulating inorganic phosphate and high levels of estrogen are strongly positively

associated with breast cancer [57], but this mechanism is more relevant for ER^{+ve} than ER^{-ve} breast cancer.

Our main analysis showed little evidence of an association between genetically predicted circulating vitamin B12 concentrations with risk of breast cancer, although one of the vitamin B12 SNPs, rs778805, was associated with risk of overall breast cancer in the BCAC GWAS and the result of the weighted median analysis was significant for overall breast cancer. A recent meta-analysis of four observational studies concluded that there was no association between serum vitamin B12 and the risk of overall breast cancer (RR: 0.73, 95% CI: 0.44 to 1.22) comparing the highest vs lowest categories [58].

The main strengths of the current MR study are the ability to circumvent biases that often plague observational studies and the utilization of data from large-scale genetic consortia. Potential limitations should be also considered in the interpretation of our findings. Conducting an MR analysis using summary association data does not allow for stratified analyses by covariates of interest such as menopausal status and body mass index. Moreover, our analysis was underpowered to identify associations of small magnitude between some nutrients and risk of breast cancer. Specifically, a minimum R^2 value of 1.5% was required in our study to capture an OR of 1.10 per SD increase in nutrient concentrations with 0.8 power, and this cutoff point was not met for folate (R^2 =1%), vitamin B6 (1%), and phosphorus (1.2%). Larger GWASs of nutrients are required to enable the construction of better genetic instruments for these nutrients. An additional limitation of our study is that the GWAS studies for the different micronutrients involved both men and women, whereas breast cancer was assessed only in women. Therefore, our results might be biased if the effects of the genetic variants are different between the two sexes.

However, a recent sex-specific GWAS study on 33 biomarkers in UK Biobank, including calcium, showed that except of testosterone most biomarkers had few or no sex-specific SNPs and for calcium in particular, no sex specific genetic variants were observed [59]. The circulating concentrations of several minerals are tightly regulated, which means that large changes in intake will not lead to detectable changes in circulating concentrations; thus, MR estimates should not be interpreted as relevant to dietary intake.

In conclusion, we conducted the first comprehensive two-sample MR study to investigate whether genetically predicted concentrations of 11 micro-nutrients are associated with risk of breast cancer. An increased risk of overall and ER^{+ve} disease was observed for genetically higher concentrations of magnesium that was robust to several different sensitivity analyses and to correction for multiple comparisons. Future studies are warranted to replicate this finding and to disentangle the potential underlying mechanisms.

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Conflict of interest: The authors declare no conflict of interest.

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Data availability: Only publicly available data were used in this study, and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

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Figure legends

Figure1. Forest plot showing results from the Mendelian randomization study to evaluate potential causal associations between 11 nutrients and breast cancer both overall and by estrogen receptor status. The odds ratios (OR) were calculated using the inverse variance weighted (IVW) method and correspond to a 1-SD increase in the concentration of the nutrients.