Association between unmetabolized folic acid and breast cancer incidence in MTHFR C677T polymorphism

Abstract

Objectives: Carriers of the C677T have both altered folate metabolism and higher risk of cancers, including breast cancer. Supplementation is thought to correct his imbalance, but high intakes of synthetic folic acid increase blood concentrations of unmetabolized folic acid (UFA) with unknown implications on breast cancer risk, particular among those with altered folate metabolism. This study assesses the association between plasma UFA and breast cancer among MTHFR C677T genotypes.

Methods: In this hospital-based case-control study, 150 adult women with confirmed history of breast cancer were age-matched to 150 adult female controls. Blood concentration of unmetabolized folic acid was determined via fasting venous blood samples and the effects of UFA on breast cancer incidence were assessed by conditional logistic regression.

Results: Stratified by genotype, we expect a small but statistically significant increased odds ratio associated with higher UFA among homozygous MTHFR C677T polymorphs and a non-statistically significant association among heterozygous genotypes between UFA and breast cancer risk. We expect to find no association of UFA and breast cancer in wild-types.

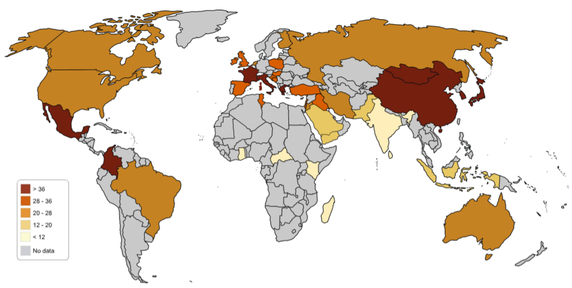
Objectives

The U.S. folic acid enrichment program has been effective in raising population average levels of folate intake and, as a consequence, in reducing incidence of neural tube defects (NTD). But, within a few years, folate intake in the population far exceeded the amount estimated prior to implementing the folic acid enrichment program and evaluated for safety.

Though it was generally believed these high intakes of folic acid were relatively harmless, research increasingly shows that folate plays a complex and potentially dual role in cancer: where too little may increase risk for carcinogenesis, but excessive levels may promote cancer growth.

Given that women of child-bearing age are the primary target of folic acid enrichment, this potential role of folate in breast cancer has been increasingly investigated among carriers of the common MTHFR C677T mutation, present in upwards of 40% of the population. However, few of these studies have sought to illuminate the potential differing affects of natural versus synthetic folate. As unmetabolized folic acid is almost exclusively a function of folic acid intake, the present study hopes to demonstrate whether high folic acid intake is associated with breast cancer in MTHFR C677T polymorphs through the association between UFA and breast cancer among the genotypes.

Worldwide distribution of MTHFR C677T T-allele [2]



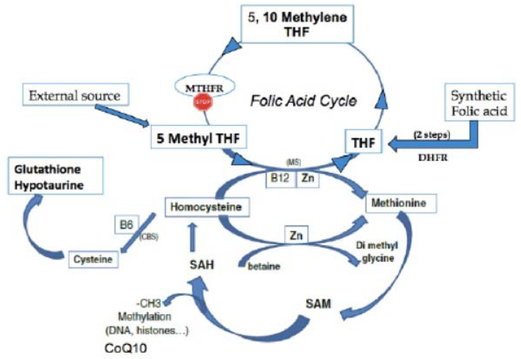
Methods

Participants for the case population will be recruited by advertisement and provider reference at three breast cancer clinics in the D.C. metropolitan area while controls will be recruited by advertisement at adjoining hospital centers. Subjects will be excluded if they are currently pregnant, lactating, taking any medication or undergoing any treatment that might interfere with folate metabolism. For the control population, additional exclusion criteria is a history of breast cancer.

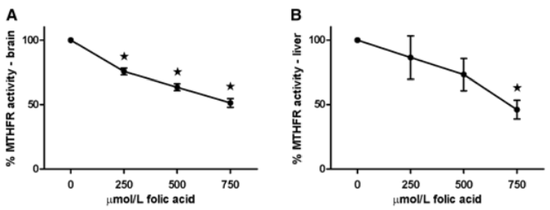
Recruited subjects will undergo a brief interview with a healthcare professional to ascertain biometrics (age, weight, height, race, menopausal status), medical history, reproductive data, and potential confounding variables (e.g. alcohol consumption). After 8 hours of fasting or more, subjects will provide venous blood samples from which genotyping and UFA may be measured.

By correlating UFA concentrations with breast cancer incidence in the MTHFR genotypes, this study aims to illustrate the potential differing affects that synthetic folate (folic acid) may have on breast cancer risk in women with altered folate metabolism via the MTHFR mutation, as compared with the risks posed by elevated folate intake from dietary sources.

The Folate Metabolism Cycle



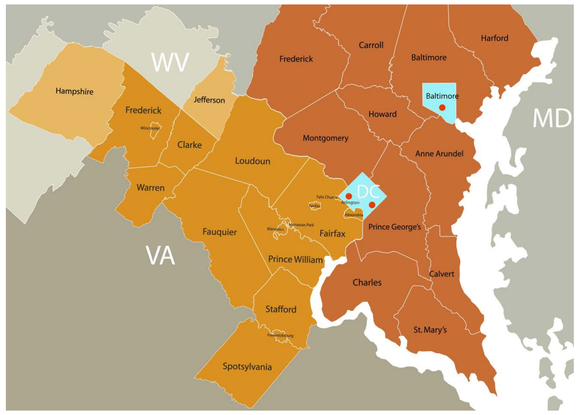
MTHFR Activity in brain extract of folic acid supplemented mice [3]

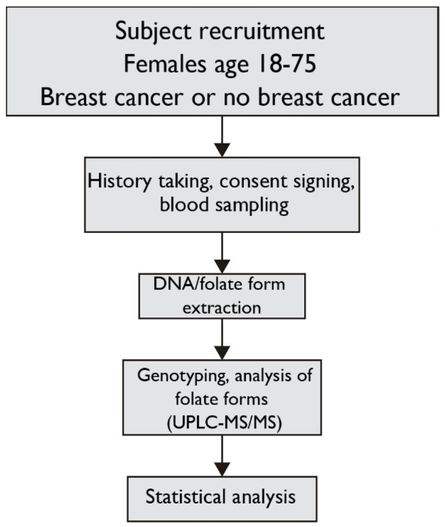


Participants

A cohort of 150 adult females with histologically confirmed breast cancer will be recruited via advertisement and referral at three breast cancer clinics; one in Washington, D.C., Maryland, and Virginia. 150 adult female controls, without a history of breast cancer will be recruited via advertisement placed in adjoining hospitals.

Participants who complete the full questionnaire, interview, and provide a blood sample will then receive explanation of compensation and reimbursement for their participation in the study. Participants will be provided $80.00 USD for both days of participation, reimbursement of travel costs to and from the hospital (up to $20.00 per day for roundtrip costs), with an additional $50.00 USD upon the provision of the blood sample.

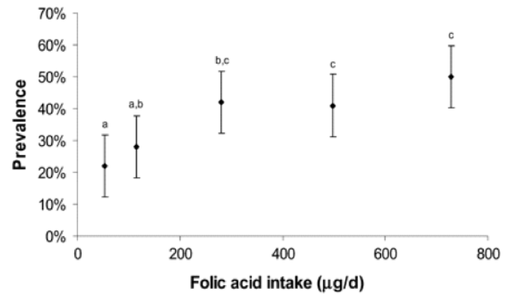




Results

Quantitative data from the study are the plasma UFA levels stratified by genotype and breast cancer status. Differences in characteristics of cases and controls will be analyzed using a Student's t-test while distribution of covariates will be tested via Chi-square test. Analyses for the interaction of genotype and UFA with breast cancer will be stratified by genotype (CC, CT, TT) and odds ratio (and 95% confidence interval) for breast cancer in relation to UFA calculated with conditional logistic regression to preserve matching.

Prevalence of UFA in relation to FA intake [4]



Discussion

It is expected that this cohort study will show a small, but statistically significant association between UFA and breast cancer among homozygous (TT) MTHFR C677T genotypes and a non-significant association among heterozygous (CT) types.

Such results provide evidence of potential harm from very elevated intakes of synthetic folates among carriers of this mutation and would warrant further investigation into risks associated with folic acid supplementation, renewed scrutiny of the safety of mandatory folic acid enrichment, and research into the possible suitability of substituting synthetic folic acid with natural 5-MTHF in enrichment and supplementation programs.

References

[2] Yadav U, Kumar P, Gupta S, Rai V. Distribution of MTHFR C677T Gene Polymorphism in Healthy North Indian Population and an Updated Meta-analysis. *Indian J Clin Biochem*. 2017; 32(4): 399–410. doi: 10.1007/s12291-016-0619-0.

[3] Christensen KE, Mikael LG, Leung KY, et al. High folic acid consumption leads to pseudo-MTHFR deficiency, altered lipid metabolism, and liver injury in mice. *Am J Clin Nutr*. 2015;101(3):646-658. doi: 10.3945/ajcn.114.086603.

[4] Morris MS, Jacques PF, Rosenberg IH, Shelhub J. Circulating unmetabolized folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. *Am J Clin Nutr.* 2010;91(6):1733-1744. doi: 10.3945/ajcn.2009.28671.

Conflict of Interest

None.