Null Results in Brief

One-Carbon Metabolism and Breast Cancer Risk: No Association of *MTHFR*, *MTR*, and *TYMS* Polymorphisms in the GENICA Study from Germany

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Introduction

Neoplastic development and growth are suspected to be influenced by availability and metabolism of folate due to effects on gene expression through DNA methylation and on genome integrity through DNA synthesis and repair (1-3). Key enzymatic regulators are methylene-tetrahydrofolate reductase (MTHFR) reducing 5,10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate, the plasma form of folate and carbon donor for the remethylation of homocysteine to methionine (4), the methionine synthase (MTR) catalyzing methylation towards *S*-adenosyl-methionine (4), and thymidylate synthase (TYMS) catalyzing both the conversion of 5,10-methylene-tetrahydrofolate to dihydrofolate and of deoxyuridylate to deoxythymidylate, a rate-limiting nucleotide of DNA synthesis (5). Common variants *MTHFR*_677_C>T Ala^{222}Val and *MTHFR*_1298_A>C Glu^{429}Ala are associated with reduced *in vitro* enzyme activity (6-8), thereby increasing the availability of folate for thymidylate and purine synthesis, affect mRNA level in case of the *TYMS*_1494_del (TAAAGT) polymorphism (9), or are thought to affect the enzymatic activity and induce modest homocysteine reduction and DNA hypomethylation in case of the *MTR*_2756_A>G Asp^{919}Gly polymorphism (10-12). Although *MTHFR* variants are associated with a decreased risk for colon cancer (13), conflicting data on their association with breast cancer exist (14-25). For this reason, we investigated *MTHFR*, *MTR*, and *TYMS* polymorphisms in a population-based breast cancer case-control study (GENICA) from Germany for their potential role in breast cancer risk.

Materials and Methods

Study Population. The GENICA breast cancer case-control study, including 688 incident cases and 724 age-matched, population-based controls from the Greater Bonn Region, Germany, has been described previously (26, 27). In brief, breast cancer cases were included based on a histopathologic diagnosis of primary breast cancer. Cases and controls were eligible if they were of Caucasian ethnicity, currently residing in the study region, and were below age 80 years. The GENICA study was approved by the Ethic's Committee of the University of Bonn. All study participants gave written informed consent.

***MTHFR*, *MTR*, and *TYMS* Genotyping.** Genomic DNA was isolated from heparinized blood samples (Puregene, Gentra Systems, Inc., Minneapolis, MN) and subjected to genotyping by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry using the Sequenom system (Sequenom, San Diego, CA) as previously described (26, 28). We analyzed the single nucleotide polymorphisms *MTHFR*_677_C>T (rs1801133), *MTHFR*_1298_A>C (rs1801131), and *MTR*_2756_A>G (rs1805087) as well as the biallelic *TYMS*_1494_del (TAAAGT) polymorphism (5).

Statistical Methods. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using SAS/STAT software, version 8.02 (29). Risk estimates for the development of breast cancer were calculated as OR with 95% CI using logistic regression analysis, conditional on age (<45, 45 to <50, 50 to <55, 55 to <60, 60 to <65, 65 to <70, ≥70 years). Potential risks were adjusted (OR_{adj}) for known risk factors, such as menopausal status (premenopausal and postmenopausal), body mass index (<20, ≥20 to <25, ≥25 to 30, ≥30), smoking status (never, former, current), history of breast cancer in mother and sisters (no/yes), parity (0 and ≥1), use of hormone replacement therapy (none, >0 to <10, ≥10 years), and use of oral contraceptives (none, >0 to <10, ≥10 years). Data were stratified for menopausal status, body mass index, smoking status, history of breast cancer in mother and sisters, parity, hormone replacement therapy, oral contraceptives, and age at first child birth (nulliparous, <20, ≥20-30, ≥30 years). Multiple testing was accounted for by Bonferroni correction. PHASE was used for the estimation of *MTHFR* haplotypes (30, 31).

Results

We obtained genotyping data at *MTHFR*_677_C>T, *MTHFR*_1298_A>C, *MTR*_2756_A>G, and *TYMS*_1494_del (TAAAGT) at a mean call rate of 96%. All genotype frequencies were in Hardy-Weinberg equilibrium. No statistically significant differences were observed between cases and

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controls. This was true for all cases and controls as well as cases and controls stratified for menopausal status (Table 1). Upon stratification of *MTHFR*_677_C>T data for smoking, history of breast cancer in mother or sister, and hormone replacement therapy use, we observed significant associations that vanished following Bonferroni correction (data not shown). This was also the case for stratifications of *MTHFR*_1298_A>C data for parity and hormone replacement therapy use, of *MTR*_2756_A>G data for body mass index and smoking, and of *TYMS*_1494_del (TAAAGT) data for body mass index (data not shown).

None of the possible genotype combinations of *MTHFR*_677_C>T, *MTHFR*_1298_A>C, *MTR*_2756_A>G, and *TYMS*_1494_del (TAAAGT) showed differences between cases and controls. When phase was established for *MTHFR* polymorphisms, we observed haplotype frequencies that differed from the expected frequencies (Table 2). A borderline significant association of *MTHFR*_677_C/*MTHFR*_1298_C and *MTHFR*_677_T/*MTHFR*_1298_A with breast cancer risk was observed (Table 2) that vanished following Bonferroni correction.

Discussion

Previous conflicting reports on an association of *MTHFR*_677_C>T and *MTHFR*_1298_A>C genotypes with breast cancer risk may be attributed to variations of study size and design, particularly ethnicity and nonsporadic breast cancers.

Table 1. Genotype frequencies of polymorphic loci in genes encoding enzymes involved in folate metabolism in breast cancer cases and controls

Polymorphism	Genotype/allele	Cases, *n* (%)	Controls, *n* (%)	OR_{adj} (95% CI)
*MTHFR*_677_C>T	All*			
	CC	249 (43)	261 (41)	1.00†,‡
	CT	274 (47)	279 (44)	1.04 (0.82-1.33)
	TT	61 (10)	93 (15)	0.69 (0.48-1.00)
	T	(32)	(37)	
	Premenopausal			
	CC	62 (44)	59 (40)	1.00§,‡
	CT	66 (47)	68 (46)	0.86 (0.51-1.44)
	TT	13 (9)	20 (14)	0.60 (0.26-1.36)
	Postmenopausal			
	CC	187 (42)	202 (42)	1.00§,‡
	CT	208 (47)	211 (43)	1.06 (0.80-1.41)
	TT	48 (11)	73 (15)	0.71 (0.47-1.09)
*MTHFR*_1298_A>C	All*			
	AA	273 (47)	295 (47)	1.00†,‡
	AC	256 (44)	266 (42)	1.04 (0.82-1.32)
	CC	53 (9)	73 (12)	0.78 (0.53-1.16)
	C	(31)	(32)	
	Premenopausal			
	AA	65 (46)	69 (47)	1.00§,‡
	AC	59 (42)	63 (43)	1.11 (0.66-1.87)
	CC	16 (11)	15 (10)	1.22 (0.53-2.77)
	Postmenopausal			
	AA	208 (47)	226 (46)	1.00§,‡
	AC	197 (45)	203 (42)	1.04 (0.79-1.37)
	CC	37 (8)	58 (12)	0.69 (0.43-1.08)
*TYMS*_1494_del TAAAGT	All*			
	ins/ins	272 (47)	292 (48)	1.00†,‡
	ins/del	245 (43)	267 (44)	0.97 (0.76-1.24)
	del/del	58 (10)	51 (8)	1.22 (0.81-1.85)
	del	(31)	(33)	
	Premenopausal			
	ins/ins	55 (40)	62 (45)	1.00§,‡
	ins/del	67 (49)	68 (49)	1.08 (0.64-1.84)
	del/del	15 (11)	9 (6)	1.82 (0.69-4.79)
	Postmenopausal			
	ins/ins	217 (50)	230 (49)	1.00§,‡
	ins/del	178 (41)	199 (42)	0.94 (0.71-1.24)
	del/del	43 (10)	42 (9)	1.13 (0.70-1.81)
*MTR*_2756_A>G	All*			
	AA	366 (63)	415 (65)	1.00†,‡
	AG	197 (34)	193 (30)	1.17 (0.91-1.49)
	GG	22 (4)	27 (4)	0.95 (0.53-1.71)
	G	(21)	(19)	
	Premenopausal			
	AA	84 (59)	89 (60)	1.00§,‡
	AG	54 (38)	48 (32)	1.34 (0.80-2.24)
	GG	4 (3)	11 (7)	0.30 (0.09-1.09)
	Postmenopausal			
	AA	282 (64)	362 (67)	1.00§,‡
	AG	143 (32)	145 (30)	1.14 (0.86-1.52)
	GG	18 (4)	16 (3)	1.36 (0.67-2.73)

*Allele frequencies are in agreement with published data (13).
†OR conditional on age in 5-year group adjusted for menopausal status, smoking status, body mass index, breast cancer in mother or sister, parity, hormone replacement therapy, and oral contraceptives.
‡Reference.
§OR conditional on age in 5-year group adjusted for smoking status, body mass index, breast cancer in mother or sister, parity, hormone replacement therapy, and oral contraceptives.

Table 2. Haplotype frequencies of *MTHFR*_677_C>T and *MTHFR*_1298_A>C in breast cancer cases and controls

*MTHFR*_677	*MTHFR*_1298	Expected frequencies (%)	Cases (%)	Controls (%)	OR* (95% CI)
C	A	44	45	40	1.00 †
C	C	21	25	28	0.80 (0.66-0.98)
T	A	24	30	32	0.81 (0.67-0.98)
T	C	11	0	0	—

*Crude ORs.
† Reference.

In our study of Caucasian women of the GENICA case-control study, we did not identify a significant association of *MTHFR* polymorphisms with breast cancer risk. Comparison of our data with those from large case-control studies (>700 study participants) of women with related ethnicity showed that also White women from the Multiethnic Cohort (20) failed to reveal a breast cancer risk association with *MTHFR* genotypes. Yet, English-speaking women of the Long Island Study showed a significant excess risk with the *MTHFR*_677_TT genotype (OR, 1.37; 95% CI, 1.06-1.78; ref. 15). However, the latter is reported to be of mixed ethnicity, and it is noteworthy that Long Island has the highest breast cancer incidence in the United States, which has been suspected to be potentially linked to environmental pollution (32). It has been shown that polycyclic aromatic hydrocarbons were associated with an increased breast cancer risk, and we may infer that these and yet other unknown environmental confounders may have contributed to that risk association. This view is in line with observations from the Shanghai Breast Cancer study, in which a significant breast cancer risk was observed as an interactive effect between *MTHFR*_677 genotypes and low folate intake being highest for *MTHFR*_677_TT (OR, 2.51; 95% CI, 1.37-4.60; ref. 25) or in the Breast Cancer Study from Korea, in which this interactive effect was seen for low intake of green vegetables (21). Dietary deficiency in folate by itself is an appraised breast cancer risk factor, and it has been shown that environmental exposures, such as alcohol intake (33-36) and estrogen (22), cause folate deficiency, thus promoting the risk to develop breast cancer.

Lack of an association of *MTHFR* polymorphisms with breast cancer risk was also observed in African American, Latino, and Hawaiian women from the aforementioned Multiethnic Cohort (20) and in smaller studies from Scotland (24); Orange County, CA (23); Korea (21); Finland (17); and Greece (19). In contrast, risk associations with *MTHFR*_677_TT were identified in Jewish women with bilateral breast cancer or combined breast cancer and ovarian cancer (18) and in familial breast cancer cases with a family history of breast cancer or bilateral breast cancer from Wessex, England (14). Although these findings seem contradictory, direct comparisons should be prohibitive due to the strong hereditary and/or familial aspects addressed in these studies. This may also refer to a small study with hospital controls and non–age matching from Turkey that showed an increased breast cancer risk with both *MTHFR* polymorphisms (16).

We confirmed known *MTHFR* haplotype frequencies (37). No association with breast cancer risk was identified for *MTR*_2756_A>G and *TYMS*_1494_del (TAAAGT) polymorphisms either alone or in combination. This is the first time that genotyping data of these DNA methylation and DNA synthesis-regulating enzymes have been provided within a breast cancer association study.

Our study has an 80% power to detect a minimum OR of 1.3 for the four polymorphisms (α = 0.05, two-sided test). Importantly, we identified a 2.8- and 3.5-fold increased breast cancer risk in the GENICA study population with respect to genotype and haplotype of the DNA repair enzyme ERCC2 (26). Our questionnaire data were insufficient with respect to an estimation of folate intake; therefore, we could not test for this association. Yet, we consider our findings of a lack of *MTHFR* genotype-associated breast cancer risk confirmatory for Caucasian women and support the notion that the observed folate intake–dependent breast cancer risk in other studies may be insignificantly contributed by *MTHFR, MTR*, and *TYMS* genotypes.

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