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Two-stage Case-control Study of *DNMT-1* and *DNMT-3B* Gene Variants and Breast Cancer Risk

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Abstract

Aberrant DNA methylation of CpG islands is a common epigenetic alteration found in cancers. DNA methylation is typically mediated by DNA methyltransferases (*DNMTs*). Only two studies have evaluated *DNMT-3B* and/or *DNMT-1* gene polymorphisms in relation to breast cancer risk, and results have been inconsistent. We comprehensively evaluated genetic variations in the *DNMT-1* and *DNMT-3B* genes with breast cancer risk among the participants of the Shanghai Breast Cancer Study (SBCS), a large-scale, two-stage, case-control study. Of the 25 SNPs in the *DNMT-1* and *DNMT-3B* genes analyzed, only one (*rs8101866*) reached a nominal significance level ($p=0.042$). This association, however, was no longer statistically significant after adjustment for multiple comparisons. Our data suggest that there is no apparent association of common *DNMT-1* and *DNMT-3B* polymorphisms with the risk of breast cancer among Chinese women.

Keywords

breast cancer; SNPs; DNMT-1; DNMT-3B; risk

Introduction

Aberrant DNA methylation of CpG islands is a common epigenetic alteration found in cancers [1]. DNA methylation is typically mediated by DNA methyltransferases (*DNMTs*). *DNMT-1* binds methyl groups to hemimethylated DNA during replication for the maintenance of methylation in the genome. *DNMT-3B* adds methyl groups to unmethylated CpG dinucleotides for *de novo* methylation [1]. Three single nucleotide polymorphisms (SNPs) in the *DNMT-3B* promoter region, –149C>T (*rs2424913*), –283T>C (*rs6058870*), and –579G>T (*rs1569686*), have been evaluated as possible genetic susceptibility factors for several types of cancer [2–7]. However, only two studies have evaluated *DNMT-3B* and/or *DNMT-1* gene polymorphisms in relation to breast cancer risk, and results have been inconsistent [5;8].

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This study was undertaken to comprehensively assess genetic variations in the *DNMT-1* and *DNMT-3B* genes, and evaluate associations of these variants with breast cancer risk among the participants of the Shanghai Breast Cancer Study (SBCS).

Materials and methods

Study population

Study subjects were participants of the SBCS, a large-scale, two-phase, population-based, case-control study conducted in urban Shanghai, which has been described previously [9;10]. Briefly, 1,459 (91.1%) cases and 1,556 (90.3%) controls from Phase 1 and 1,989 cases (83.7%) and 1,989 controls (70.4%) from Phase 2 completed in-person interviews. Blood or buccal cell samples were donated by 1,193 cases (81.8%) and 1,310 controls (84.2%) from Phase 1 and 1,932 (97.1%) cases and 1,857 (93.4%) controls from Phase 2. Approval of the study was granted by the relevant review boards in both China and the United States, and written, informed consent was obtained from all participants prior to interview.

Genotyping

Haplotype tagging SNPs (htSNPs) were selected from the Han Chinese data included in the HapMap Project [11] using the Tagger program [12] to capture SNPs with a minimum minor allele frequency (MAF) of 0.05 in either *DNMT-1* or *DNMT-3B* (± 5 kb) with an r^2 of 0.90 or greater. Known or potentially functional SNPs were forced into the htSNP selection process. Eight SNPs for the *DNMT-1* gene and 7 SNPs for the *DNMT-3B* gene were selected in 2006, and were evaluated in 1,062 cases and 1,069 controls from Phase 1, using a Targeted Genotyping System (Affymetrix, Santa Clara, CA) as previously described [13].

One SNP with a potentially interesting result from Phase 1 (*rs6058869*) was selected for additional genotyping using a TaqMan assay (assay ID, C__30018043_10) for 1,919 cases and 1,820 controls from Phase 2. The laboratory staff was blinded to the identity of the samples. Quality control (QC) samples were included in the genotyping assays [10]. The concordance rate for the blinded samples was 97.5%.

To increase the density of genetic markers in this study, data from our recently completed Affymetrix Genome-Wide Human SNP Array 6.0 was included for an additional 6 SNPs for the *DNMT-1* gene (± 10 kb) and 26 SNPs for the *DNMT-3B* gene (± 10 kb) for 4,157 participants, including 1,104 cases and 1,109 controls from Phase 1 and 969 cases and 975 controls from Phase 2.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was tested by comparing the observed and expected genotype frequencies of the controls (χ^2 -test). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were determined by logistic regression analyses using additive models that included adjustment for age, education, and study phase, when appropriate. All statistical tests were two-tailed, and p-values were considered to be statistically significant when ≤ 0.05 .

Results

A total of 6,031 women were included in the current study: 2,291 Phase 1 participants and 3,740 Phase 2 participants. Women in both study phases were generally comparable (data not shown). As expected, breast cancer cases were found to differ from controls in regards to known breast cancer risk factors. Cases were more likely to have an earlier age at menarche,

older age at first live birth, a history of breast fibroadenomas, a history of breast cancer in a first degree relative, a higher BMI or WHR, and they were less likely to participate in regular physical activity than controls (data not shown).

A total of 47 SNPs were genotyped in the current study, however, of these, 20 were found to have MAFs of less than 0.05 in our study population (*rs2424906*, *rs17123571*, *rs2424907*, *rs6119951*, *rs6058880*, *rs6058883*, *rs6058887*, *rs2424913*, *rs6119285*, *rs1040555*, *rs8115360*, *rs6057648*, *rs2424921*, *rs2424930*, *rs6119967*, *rs7263832*, *rs6058897*, *rs437302*, *rs406193*, and *rs242542*), and two were found to deviate from HWE in controls (*rs8111085* and *rs16999358*). These 22 SNPs were excluded from the analysis. Therefore, 12 SNPs in the *DNMT-1* gene and 13 SNPs in the *DNMT-3B* gene were included in the analyses. The linkage disequilibrium structure of the 25 polymorphic loci is shown in Fig. 1.

As shown in Table 1, associations with breast cancer risk were evaluated among 2,131 participants from Phase 1 for 11 SNPs, among 4,157 participants from Phase 1 and Phase 2 for an additional 14 SNPs from the Genome-Wide Human SNP Array 6.0, and among 5,870 Phase 1 and Phase 2 participants for one SNP with an interesting preliminary result that was selected for validation (*DNMT-3B rs6058869*). This SNP and others with potentially interesting results are shown stratified by SBCS study phase in Table 2. Four SNPs (*rs11085587*, *rs6058869*, *rs4911259*, and *rs6058893*) with significant effects among Phase 1 participants were found to not have consistent results among Phase 2 participants. Although the variant allele of *rs8101866* was associated with increased breast cancer risk in combined analyses ($p = 0.042$), the association was not statistically significant after adjusting for multiple comparisons.

Discussion

Of the 25 SNPs in the *DNMT-1* and *DNMT-3B* genes analyzed in this large, two-stage, case-control study, only one (*rs8101866*) was reached a normal significance level ($p=0.042$). This association, however, was no longer statistically significant after adjustment for multiple comparisons. Given the size of our study population, at the $p = 0.05$ significance level, this analysis had a greater than 93% power to detect an OR of 1.3 for a SNP with a MAF of 0.10, greater than 76% power to detect an OR of 1.2 for a SNP with a MAF of 0.15, and greater than 81% power to detect an OR of 1.2 for a SNP with a MAF of 0.20.

DNA methylation plays a significant role in the development and progression of various cancers, and *DNMTs* are crucial for DNA methylation. Increased *DNMT-1* and *DNMT-3B* activity has been detected in several tumors, indicating that these two genes may contribute to tumorigenesis [5;14–16]. Three *DNMT-3B* SNPs have been previously evaluated in relation to cancer risk. Located in the promoter, the *DNMT-3B* –149 C>T (*rs2424913*) polymorphism has been shown to result in a 30% increase in promoter activity [17]. Carriers of the T allele have been reported to have significantly increased risk of lung, prostate, and head and neck cancers [6;7;18]. However, the C allele has been associated with an increased risk of breast cancer among British women in a small case-control study (352 cases and 258 controls) [5]. This SNP was not genotyped in the current study due to its low MAF among Han Chinese (MAF = 0.011) (www.hapmap.org). Another functional *DNMT-3B* SNP, –283 T>C (*rs6058870*), has been shown to result in approximately 50% decreased promoter activity in *in vitro* analyses. Furthermore, the lower activity T allele has been associated with a decreased risk of lung cancer [3]. A third polymorphism, –579 G>T (*rs1569686*), which does not change promoter activity, has been associated with susceptibility to colorectal cancer [2]. Neither of these SNPs were included in the HapMap project, and therefore were not selected for genotyping in the current study. The coverage of genetic variations of these two genes is high, since the SNPs that were included in the current study

were selected based on HapMap SNPs with a MAF greater than 0.05 and an r^2 of 0.90 or greater in these two genes. *DNMT-1* gene polymorphisms have not been previously reported in relation to breast cancer risk. In our study, no *DNMT-1* or *DNMT-3B* polymorphisms were significantly associated with breast cancer risk. In a study conducted among 4,474 breast cancer cases and 4,580 controls, Cebrian et al. [8] observed no association with any SNPs or common haplotypes of the *DNMT-1* gene with breast cancer risk. One SNP (*rs406193*) in the *DNMT-3B* gene was significantly associated with breast cancer risk (P -trend = 0.003). This association, however, was no longer statistically significant after adjustment for multiple comparisons (P -trend = 0.124) [8]. Moreover, no association with any common haplotypes of the *DNMT-3B* gene and breast cancer risk was observed [8].

Strengths of our study include its comprehensive and systematic approach to characterizing genetic variations across the *DNMT-1* and *DNMT-3B* genes. Further, a two-stage design was used to reduce type I errors, and the sample sizes in both stages were large, so that type II errors were also reduced. The population-based, case-control study design and high participation rate minimized selection bias. The strong design of the study lends credibility to our findings that there is no apparent association of common *DNMT-1* and *DNMT-3B* polymorphisms with the risk of breast cancer among Chinese women.

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Abbreviations

CI	confidence interval
DNMT	DNA methyltransferase
htSNPs	haplotype tagging SNPs
HWE	Hardy-Weinberg equilibrium
LD	linkage disequilibrium
MAF	minor allele frequency
QC	quality control
SNP	single nucleotide polymorphism

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Fig 1. Linkage disequilibrium structure of *DNMT-1* (A) and *DNMT-3B* (B) SNPs. Value shown is r^2 .

Table 1

DNMT-1 and *DNMT-3B* gene variants and breast cancer risk, the Shanghai Breast Cancer Study

Gene, SNP	Alleles [*]	Region	Method [†]	Study Phase [‡]	MAF (%) [‡]	HWE ^{‡‡}	Breast Cancer Risk, OR (95% CI) [§]		
							AB [§]	BB [§]	p-value [§]
<i>DNMT-1</i>									
rs2116940	A/G	promoter	Both	1 & 2	44.8	0.415	1.0 (0.9–1.1)	0.9 (0.8–1.1)	0.398
rs2336691	G/A	intron 1	Targeted	1	9.6	0.952	1.1 (0.9–1.3)	1.3 (0.6–2.8)	0.388
rs7253062	G/A	intron 1	Targeted	1	39.8	0.822	0.9 (0.8–1.1)	1.0 (0.7–1.4)	0.586
rs16999593	T/C	exon 4	Targeted	1	28.5	0.326	1.1 (0.9–1.3)	0.8 (0.5–1.3)	0.812
rs6511685	T/A	intron 5	Targeted	1	19.1	0.192	1.0 (0.8–1.2)	1.2 (0.9–1.7)	0.501
rs6511677	G/A	intron 9	Affy 6.0	1 & 2	25.5	0.850	0.9 (0.8–1.0)	1.0 (0.8–1.3)	0.293
rs8101866	T/C	intron 10	Affy 6.0	1 & 2	27.1	0.693	1.1 (1.0–1.2)	1.3 (1.0–1.6)	0.042
rs2241531	C/G	intron 13	Targeted	1	44.3	0.909	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.708
rs10418707	G/A	intron 27	Affy 6.0	1 & 2	44.4	0.425	1.0 (0.9–1.1)	0.9 (0.8–1.1)	0.432
rs10407514	C/G	intron 27	Affy 6.0	1 & 2	46.6	0.501	1.0 (0.9–1.2)	0.9 (0.8–1.1)	0.469
rs4804122	T/C	3' FR//	Affy 6.0	1 & 2	28.1	0.969	0.9 (0.8–1.0)	1.0 (0.8–1.2)	0.175
rs11085587	G/C	3' FR//	Affy 6.0	1 & 2	28.1	0.536	1.1 (0.9–1.2)	1.3 (1.0–1.6)	0.049
<i>DNMT-3B</i>									
rs6058869	T/C	promoter	Targeted/Taqman	1 & 2	7.7	0.578	1.1 (1.0–1.3)	0.7 (0.3–1.4)	0.203
rs242908	T/C	intron 1	Targeted	1	40.2	0.871	1.1 (0.9–1.3)	1.2 (0.9–1.5)	0.204
rs6119954	G/A	intron 1	Affy 6.0	1 & 2	31.2	0.936	1.0 (0.9–1.2)	1.0 (0.8–1.3)	0.800
rs6141813	A/G	intron 1	Both	1 & 2	34.2	0.366	1.0 (0.9–1.2)	1.0 (0.8–1.2)	0.744
rs4911108	G/A	intron 6	Targeted	1	7.5	0.078	1.3 (1.0–1.6)	0.6 (0.2–1.8)	0.201
rs4911259	G/T	intron 6	Affy 6.0	1 & 2	7.6	0.326	1.2 (1.0–1.4)	0.4 (0.2–1.1)	0.200
rs910084	T/C	intron 8	Affy 6.0	1 & 2	7.7	0.245	1.2 (1.0–1.4)	0.5 (0.2–1.2)	0.393
rs6088008	G/A	intron 10	Affy 6.0	1 & 2	7.6	0.371	1.1 (1.0–1.4)	0.5 (0.2–1.3)	0.394
rs998382	G/A	intron 12	Affy 6.0	1 & 2	7.5	0.192	1.2 (1.0–1.4)	0.5 (0.2–1.2)	0.367
rs4911110	G/A	intron 20	Affy 6.0	1 & 2	7.5	0.311	1.2 (1.0–1.4)	0.5 (0.2–1.3)	0.246
rs6058893	T/C	intron 20	Affy 6.0	1 & 2	7.6	0.061	1.2 (1.0–1.4)	0.5 (0.2–1.1)	0.271
rs6058896	C/T	3' UTR	Both	1 & 2	7.1	0.236	1.2 (1.0–1.4)	0.5 (0.2–1.3)	0.225
rs8118663	G/A	3' FR//	Affy 6.0	1 & 2	41.7	0.415	1.1 (0.9–1.2)	1.1 (0.9–1.3)	0.324

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* Major/minor alleles as determined by allele frequency among genotyped controls

[†] Genotyping method and SBCS study phase: Affymetrix Targeted Genotyping among 1,062 cases and 1,069 controls from SBCS Phase 1 and/or TaqMan Targeted Genotyping among 1,919 cases and 1,820 controls from SBCS Phase 2 (Targeted), or Affymetrix 6.0 genotyping among 1,104 cases and 1,109 controls from Phase 1, and 965 cases and 971 controls from SBCS Phase 2 (Affy 6.0), or genotyped by both methods (Both); study phases 1&2 show pooled estimates

[‡] Minor allele frequency among all genotyped controls

^{§§} Hardy-Weinberg equilibrium test, p-value among controls

[§] Risk of breast cancer, adjusted for age, education, and study phase (when appropriate); AA major allele homozygotes (reference group), AB heterozygotes, BB minor allele homozygotes; p-value for trend from additive models

//₃’ FR: downstream flanking region, 3’ of the gene

Bold values considered to be significant at p 0.05

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Table 2
Association of selected *DNMT-1* and *DNMT-3B* gene polymorphisms with breast cancer risk, by SBCS study phase

Gene, SNP	Alleles*	Region	Method [†]	MAF (%) [‡]	Phase 1 OR (95% CI) [§]			Phase 2 OR (95% CI) [§]			Combined OR (95% CI) [§]		
					AB [§]	BB [§]	p-value [§]	AB [§]	BB [§]	p-value [§]	AB [§]	BB [§]	p-value [§]
<i>DNMT-1</i>													
rs8101866	T/C	intron 10	Affy 6.0	27.1	1.0 (0.8–1.2)	1.3 (1.0–1.9)	0.196	1.2 (1.0–1.4)	1.2 (0.8–1.7)	0.111	1.1 (1.0–1.2)	1.3 (1.0–1.6)	0.042
rs4804122	T/C	3' FR//	Affy 6.0	28.1	0.9 (0.7–1.0)	0.9 (0.6–1.3)	0.209	0.9 (0.7–1.1)	1.0 (0.7–1.4)	0.460	0.9 (0.8–1.0)	1.0 (0.8–1.2)	0.175
rs11085587	G/C	3' FR//	Affy 6.0	28.1	1.0 (0.8–1.2)	1.4 (1.0–2.0)	0.121	1.1 (0.9–1.4)	1.1 (0.8–1.6)	0.214	1.1 (0.9–1.2)	1.3 (1.0–1.6)	0.049
<i>DNMT-3B</i>													
rs6058869	T/C	promoter	Targeted/Tagman	7.7	1.3 (1.0–1.7)	0.8 (0.3–2.3)	0.076	1.1 (0.9–1.3)	0.5 (0.2–1.5)	0.812	1.1 (1.0–1.3)	0.7 (0.3–1.4)	0.203
rs4911259	G/T	intron 6	Affy 6.0	7.6	1.4 (1.1–1.8)	0.6 (0.2–1.6)	0.061	1.0 (0.8–1.3)	0.3 (0.1–1.3)	0.668	1.2 (1.0–1.4)	0.4 (0.2–1.1)	0.200
rs6058893	T/C	intron 20	Affy 6.0	7.6	1.4 (1.1–1.8)	0.5 (0.2–1.6)	0.043	1.0 (0.8–1.3)	0.2 (0.0–1.6)	0.731	1.2 (1.0–1.4)	0.5 (0.2–1.1)	0.271

* Major/minor alleles as determined by allele frequency among genotyped controls

[†] Genotyping method: Affymetrix Targeted Genotyping among 1,062 cases and 1,069 controls from SBCS Phase 1 and TaqMan Targeted Genotyping among 1,919 cases and 1,820 controls from SBCS Phase 2 (Targeted), or Affymetrix 6.0 genotyping among 1,104 cases and 1,109 controls from Phase 1, and 965 cases and 971 controls from SBCS Phase 2 (Affy 6.0)

[§] Breast cancer risk odds ratios and 95% confidence intervals from additive models, adjusted for age, education, and study phase (when appropriate), p-value for trend from additive effect models

// 3' FR: downstream flanking region, 3' of the gene

Bold values considered to be significant at p 0.05