Published in final edited form as:
Breast Cancer Res Treat. 2010 June ; 121(2): 445–452. doi:10.1007/s10549-009-0579-7.

E-cadherin polymorphisms and breast cancer susceptibility: a report from the Shanghai Breast Cancer Study

Alicia Beeghly-Fadiel[1], **Wei Lu**[2], **Yu-Tang Gao**[3], **Jirong Long**[1], **Sandra L. Deming**[1], **Qiuyin Cai**[1], **Ying Zheng**[2], **Xiao-ou Shu**[1], and **Wei Zheng**[1]

Wei Zheng: wei.zheng@vanderbilt.edu

[1] Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Institute of Medicine and Public Health, Vanderbilt University Medical Center, Vanderbilt University School of Medicine, 2525 West End Avenue, 8th Floor, Nashville, TN 37203-1738, USA

[2] Shanghai Center for Disease Control and Prevention, Shanghai, China

[3] Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

Abstract

The epithelial transmembrane glycoprotein *E-cadherin* (*CDH1*) is necessary for intercellular adhesion, cell signaling, and maintenance of cellular differentiation; reduced expression contributes to cell proliferation, invasion, and cancer progression. Functional or potentially functional single nucleotide polymorphisms (SNPs) in *E-cadherin* have been previously identified and evaluated in relation to cancer risk; however, studies on breast cancer have been sparse. Forty-six SNPs were genotyped to capture genetic variation of the *CDH1* gene among 2,290 Phase 1 and 1,944 Phase 2 participants of the Shanghai Breast Cancer Study (SBCS), a large, population-based, case–control study. No overall associations between *E-cadherin* SNPs and breast cancer risk were observed. When stratified by menopausal status, associations that were consistent between Phases 1 and 2 and significant when data from both phases were combined were observed for several SNPs. Although none of these associations retained statistical significance after correcting for the total number of polymorphisms evaluated, this study suggests that genetic variation in *CDH1* may be associated with breast cancer risk, and that this relationship may vary by menopausal status.

Keywords

E-cadherin; Polymorphisms; Breast cancer risk

Introduction

The transmembrane glycoprotein *E-cadherin* (*CDH1*) is necessary for normal epithelial cells intercellular adhesion, cell polarity, cell signaling, and maintenance of cellular differentiation and tissue morphology [1–3]. Diminished *E-cadherin* expression promotes malignant transformation, tumor invasion, and metastasis [1–3]. A promoter polymorphism (*−160 C/A*, *rs16260*) that results in reduced *E-cadherin* expression for the minor allele (*A*) [4–6] has been extensively studied and is suggested to be associated with increased susceptibility to lung, prostate, and gastric cancers in meta-analyses [7,8]. In regards to breast cancer, only two case–control studies have evaluated this single nucleotide polymorphism (SNP); one found no association [5], while the other found a significantly increased risk among *A* allele carriers

Correspondence to: Wei Zheng, wei.zheng@vanderbilt.edu.

[9]. Additional promoter polymorphisms that influence *E-cadherin* expression have also been reported (*−347 G/GA*, *−288 T/−*, *−285 C/A*, *−54 G/C*) [10,11], as have other potentially functional SNPs (*163 + 37235 G/A* in intron 2, and *3′ UTR + 54 C/T*) [12,13], but none have been evaluated in relation to breast cancer risk. This study was, therefore, undertaken to comprehensively assess individual genetic variation across *E-cadherin*, and evaluate associations with susceptibility to breast cancer among participants of the Shanghai Breast Cancer Study (SBCS).

Methods

Study subjects were participants of the SBCS, a large, two-phase, population-based, case–control study of women in urban Shanghai which has been previously described in detail [14–16]. Briefly, breast cancer cases were identified via a rapid case-ascertainment system in Phase 1, and the Shanghai Cancer Registry in Phases 1 and 2; diagnoses were confirmed by two senior pathologists. Controls were randomly selected using the Shanghai Resident Registry. Phase 1 recruitment occurred between August 1996 and March 1998, and included women aged 25–65. Phase 2 recruitment occurred from April 2002 to February 2005 and was expanded to include women aged 20–70. In-person interviews were completed for 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. Blood samples were donated by 1,193 cases (81.8%) and 1,310 controls (84.2%) from Phase 1 and blood or buccal cell samples were donated by 1,932 (97.1%) cases and 1,857 (93.4%) controls from Phase 2. Approval was granted from relevant review boards in both China and the United States.

Haplotype tagging SNPs (htSNPs) were selected using Han Chinese data presented in the HapMap Project [17] using the Tagger program [18] to capture SNPs with a minimum minor allele frequency (MAF) of 0.05 in *E-cadherin* (±5 kb) with an r^2 of 0.90 or greater. Twenty-eight *E-cadherin* SNPs were selected; twenty-four were successfully designed and genotyped in 2006 for 1,062 cases and 1,069 controls from Phase 1, using a Targeted Genotyping System (Affymetrix, Santa Clara, CA) as previously described [15]. In order to increase the density of genetic markers in this study, data from our recently completed Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix) was included for an additional 22 *E-cadherin* polymorphisms (±10 kb) that were genotyped among 1,104 cases and 1,109 controls from Phase 1, and 969 cases and 975 controls from Phase 2.

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 models that included adjustment for age, education, and study phase if appropriate. Additive, dominant, recessive, and allelic associations were considered. Linkage disequilibrium (LD) was assessed by Haploview [19]. Haplotype analysis was conducted with Hapstat [20]. Initial statistical significance was determined with a threshold *P* value of 0.05; however, to address the issue of multiple comparisons, the Bonferroni correction was then employed. All statistical tests were two-tailed.

Results

A total of 4,234 women were included in this study: 2,290 Phase 1 participants and 1,944 Phase 2 participants (Table 1). Women in both study phases were generally comparable. 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 earlier age at menarche, older age at first live birth, a history of breast fibroadenomas, a history of breast cancer among a first degree relative, a

higher body mass index (BMI) and/or waist-to-hip ratio (WHR), and less likely to participate in regular physical activity than controls.

A total of 46 *E-cadherin* SNPs were included in this study: 24 htSNPs and 22 additional SNPs from the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix). Of these polymorphisms, none were found to deviate from HWE, but six were found to have minor allele frequencies (MAFs) of less than 5% (*rs7194684*, *rs3931740*, *rs8049967*, *rs7190460*, *rs13330170*, and *rs2276328*). Eleven SNPs were included by both genotyping methods included in this study for an average of 1,895 participants; concordance rates for these samples ranged from 99.6–100, and averaged 99.78. When two genotyping sources were available for one polymorphism, the source with the larger number of samples genotyped was used in our analyses. Information and estimates of effect for the 40 *E-cadherin* polymorphisms with MAF $\geq$ 5% are shown in Table 2. In analyses including all women, no SNPs were found to be significantly associated with breast cancer risk in additive models that included adjustment for age, education, and study phase (when appropriate). Further, no significant associations were identified under dominant or recessive models (data not shown). For simplification, estimates of effect on risk per minor allele are presented.

As the etiology of breast cancer may differ by menopausal status, stratified analysis was conducted. Several *CDH1* SNPs appeared to be associated with breast cancer risk among either pre- or postmenopausal women. Again, additive, dominant, and recessive models were considered, while for simplification, allelic associations are presented in Table 2. Polymorphisms of interest were then selected for further analysis to address whether associations with breast cancer risk were consistent when stratified by study phase (Table 3); models best suited to each SNP are presented. Among premenopausal women, three SNPs (*rs2059254*, *rs9925923*, and *rs12919719*) were consistently associated with increased risk in dominant models, whereas one SNP (*rs7188750*) was consistently associated with decreased risk in a recessive manner. Among postmenopausal women, four SNPs (*rs9989407*, *rs7196495*, *rs7196661*, and *rs13689*) were consistently associated with increased risk in recessive models, and five SNPs (*rs2059254*, *rs9925923*, *rs12919719*, *rs12599393*, and *rs1862748*) were consistently associated with decreased risk in a dominant manner. However, no associations retained statistical significance after adjusting for multiple comparisons. In order to further evaluate the hypothesis that the association between *E-cadherin* SNPs and breast cancer may differ in estrogen-related conditions, stratification by dichotomized BMI was also conducted; no associations were seen (data not shown).

The LD structure of the 40 polymorphic *E-cadherin* SNPs evaluated in the current study is shown in Fig. 1. This LD structure included 2,152 genotyped controls and contained seven haplotype blocks. No associations with breast cancer risk were found in analyses among all women. However, *E-cadherin* haplotypes and breast cancer risk seemed to be associated in analysis that included only either pre- or postmenopausal women (data not shown). In general, haplotype analysis was consistent with the results from single SNP analysis.

Discussion

Common genetic variation across the *E-cadherin* gene was systematically evaluated in a large, population-based study of Chinese women. A total of 46 SNPs were genotyped; no overall associations with breast cancer risk were observed among 2,083 cases and 2,152 controls. In addition to polymorphisms, many other common *CDH1* alterations have been reported, including mutations, loss of heterozygosity, transcriptional repression, and epigenetic silencing [3]. If present, these mechanisms of *E-cadherin* loss could dilute any effects due to SNPs on breast cancer risk, possibly explaining our results. However, several associations with breast cancer risk were observed when the study population was stratified by menopausal status; many

were consistent between study phases. Differences in the relationship between *CDH1* polymorphisms and breast cancer risk by menopausal status could result from the complex interaction between *E-cadherin* and the estrogen pathway [21].

A classical tumor suppressor, *E-cadherin* expression has been shown to be frequently reduced or lost among epithelial tumors [2,3]. This results in the suboptimal regulation of cell–cell adhesion, loss of cellular polarity, tissue disorganization, tumor progression, and metastasis [1,3]. Roles in tumor initiation have also been suggested, as the loss of *E-cadherin* may promote tumorigenesis by releasing membrane-bound *β*-catenin, thereby, potentiating the canonical Wnt signaling pathway, or by modulating mitogenic signaling, such as EGF-induced cellular proliferation [1]. Several functional polymorphisms that diminish *E-cadherin* expression have been reported [4,6,10,11]; however, studies on breast cancer risk have been sparse. Yu et al. genotyped the functional promoter polymorphisms *−160 C/A* (*rs16260*) and *−347 G/GA* among 468 cases and 470 controls and found that the two SNPs were in high LD [9]. They found a significant dominant effect, such that minor allele carriers (*rs16260 A*) were 30% more likely to be breast cancer cases than women with only the major allele (*C*) [9]. On the contrary, Lei et al. genotyped the *−160 C/A* (*rs16260*) SNP among 576 cases and 348 controls, and found no association with breast cancer risk [5]. While not directly genotyped in this study, the genetic variation of this polymorphism was captured; three genotyped SNPs (*rs11865026*, *rs8056538*, and *rs12930371*) are reported to be in perfect LD ($D' = 1.0$, $r^2 = 1.0$) with *rs16260* [17]. None of these three SNPs were associated with breast cancer risk, either among all women, or when stratified by menopausal status, in this study.

Several *E-cadherin* polymorphisms were found to be associated with breast cancer risk in analyses stratified by menopausal status, and significant when data from both study phases were combined. Among premenopausal women, a modest increase in risk was associated with three SNPs in intron 2, while a larger protective effect was observed for an SNP in intron 5. Among postmenopausal women, a large increase in risk was seen for SNPs in the promoter, intron 2, and 3′ UTR, while a modest decrease in risk was associated with five SNPs in intron 2. However, several considerations must be made in interpreting these results. First, it must be noted that the sample size of this stratified analysis was reduced, and the smallest number of participants that was included was for those SNPs assayed by Affymetrix Targeted Genotyping among postmenopausal women (345 cases and 377 controls). In addition, when considering the number of associations evaluated, a Bonferroni corrected *P* value of 0.00125 would replace the 0.05 threshold for statistical significance; none of our estimates met this level of significance.

Strengths of this study include a large, two-phase, population-based study. We also had excellent coverage of the genetic variation across *E-cadherin*, as the polymorphisms that we genotyped are estimated to cover 100% of the SNPs with MAFs of 5% or greater with an r^2 of 0.8. Further, we had greater than 89% power to detect the association of 1.3 or greater for an SNP with an MAF of 15%, should such an association exist. In summary, several *CDH1* SNPs were found to be differentially associated with pre- and postmenopausal women, with consistent results between our two study phases. Additional studies are warranted to evaluate the association between *E-cadherin* polymorphisms and breast cancer susceptibility.

Acknowledgments

This research was supported by USPHS grants R01CA64277, R01CA90899, and R01CA124558. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The authors wish to thank the participants and research staff of the Shanghai Breast Cancer Study for their contributions and commitment to this project, and Brandy Venuti for assistance with the preparation of this manuscript. Sample preparation and genotyping assays, using Affymetrix arrays, were conducted

at the Survey and Biospecimen Shared Resource and the Vanderbilt Microarray Shared Resource, respectively, which are supported in part by the Vanderbilt-Ingram Cancer Center (P30CA68485).

References

1. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: how does cadherin dysfunction promote tumor progression? Oncogene 2008;27:6920–6929. [PubMed: 19029934]
2. van RF, Berx G. The cell–cell adhesion molecule *E-cadherin*. Cell Mol Life Sci 2008;65:3756–3788. [PubMed: 18726070]
3. Baranwal S, Alahari SK. Molecular mechanisms controlling *E-cadherin* expression in breast cancer. Biochem Biophys Res Commun 2009;384:6–11. [PubMed: 19379710]
4. Li LC, Chui RM, Sasaki M, Nakajima K, Perinchery G, Au HC, et al. A single nucleotide polymorphism in the *E-cadherin* gene promoter alters transcriptional activities. Cancer Res 2000;60:873–876. [PubMed: 10706097]
5. Lei H, Sjoberg-Margolin S, Salahshor S, Werelius B, Jandakova E, Hemminki K, et al. CDH1 mutations are present in both ductal and lobular breast cancer, but promoter allelic variants show no detectable breast cancer risk. Int J Cancer 2002;98:199–204. [PubMed: 11857408]
6. Cattaneo F, Venesio T, Molatore S, Russo A, Fiocca R, Frattini M, et al. Functional analysis and case–control study of −160C/A polymorphism in the *E-cadherin* gene promoter: association with cancer risk. Anticancer Res 2006;26:4627–4632. [PubMed: 17201188]
7. Wang GY, Lu CQ, Zhang RM, Hu XH, Luo ZW. The *E-cadherin* gene polymorphism 160C→A and cancer risk: A HuGE review and meta-analysis of 26 case–control studies. Am J Epidemiol 2008;167:7–14. [PubMed: 17971340]
8. Qiu LX, Li RT, Zhang JB, Zhong WZ, Bai JL, Liu BR, et al. The *E-cadherin* (CDH1)−160 C/A polymorphism and prostate cancer risk: a meta-analysis. Eur J Hum Genet 2009;17:244–249. [PubMed: 18781193]
9. Yu JC, Hsu HM, Chen ST, Hsu GC, Huang CS, Hou MF, et al. Breast cancer risk associated with genotypic polymorphism of the genes involved in the estrogen-receptor-signaling pathway: a multigenic study on cancer susceptibility. J Biomed Sci 2006;13:419–432. [PubMed: 16502042]
10. Nakamura A, Shimazaki T, Kaneko K, Shibata M, Matsumura T, Nagai M, et al. Characterization of DNA polymorphisms in the *E-cadherin* gene (CDH1) promoter region. Mutat Res 2002;502:19–24. [PubMed: 11996968]
11. Shin Y, Kim IJ, Kang HC, Park JH, Park HR, Park HW, et al. The *E-cadherin* −347G→GA promoter polymorphism and its effect on transcriptional regulation. Carcinogenesis 2004;25:895–899. [PubMed: 14729585]
12. Tsai FJ, Wu HC, Chen HY, Lu HF, Hsu CD, Chen WC. Association of *E-cadherin* gene 3′-UTR C/T polymorphism with calcium oxalate stone disease. Urol Int 2003;70:278–281. [PubMed: 12740491]
13. Nasri S, More H, Graziano F, Ruzzo A, Wilson E, Dunbier A, et al. A novel diffuse gastric cancer susceptibility variant in *E-cadherin* (CDH1) intron 2: a case control study in an Italian population. BMC Cancer 2008;8:138. [PubMed: 18482459]
14. Gao YT, Shu XO, Dai Q, Potter JD, Brinton LA, Wen W, et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. Int J Cancer 2000;87:295–300. [PubMed: 10861490]
15. Beeghly-Fadiel A, Long JR, Gao YT, Li C, Qu S, Cai Q, et al. Common MMP-7 Polymorphisms and Breast Cancer Susceptibility: A Multistage Study of Association and Functionality. Cancer Res 2008;68:6453–6459. [PubMed: 18648013]
16. Zheng W, Long J, Gao YT, Li C, Zheng Y, Xiang YB, et al. Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 2009;41:324–328. [PubMed: 19219042]
17. The International HapMap Project. Nature 2003;426:789–796. [PubMed: 14685227]
18. de Bakker PIW, McVean G, Sabeti PC, Miretti MM, Green T, Marchini J, et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. Nat Genet 2006;38:1166–1172. [PubMed: 16998491]

19. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;21:263–265. [PubMed: 15297300]

20. Lin DY, Zeng D, Millikan R. Maximum likelihood estimation of haplotype effects and haplotype-environment interactions in association studies. Genet Epidemiol 2005;29:299–312. [PubMed: 16240443]

21. Oesterreich S, Deng W, Jiang S, Cui X, Ivanova M, Schiff R, et al. Estrogen-mediated down-regulation of *E-cadherin* in breast cancer cells. Cancer Res 2003;63:5203–5208. [PubMed: 14500345]

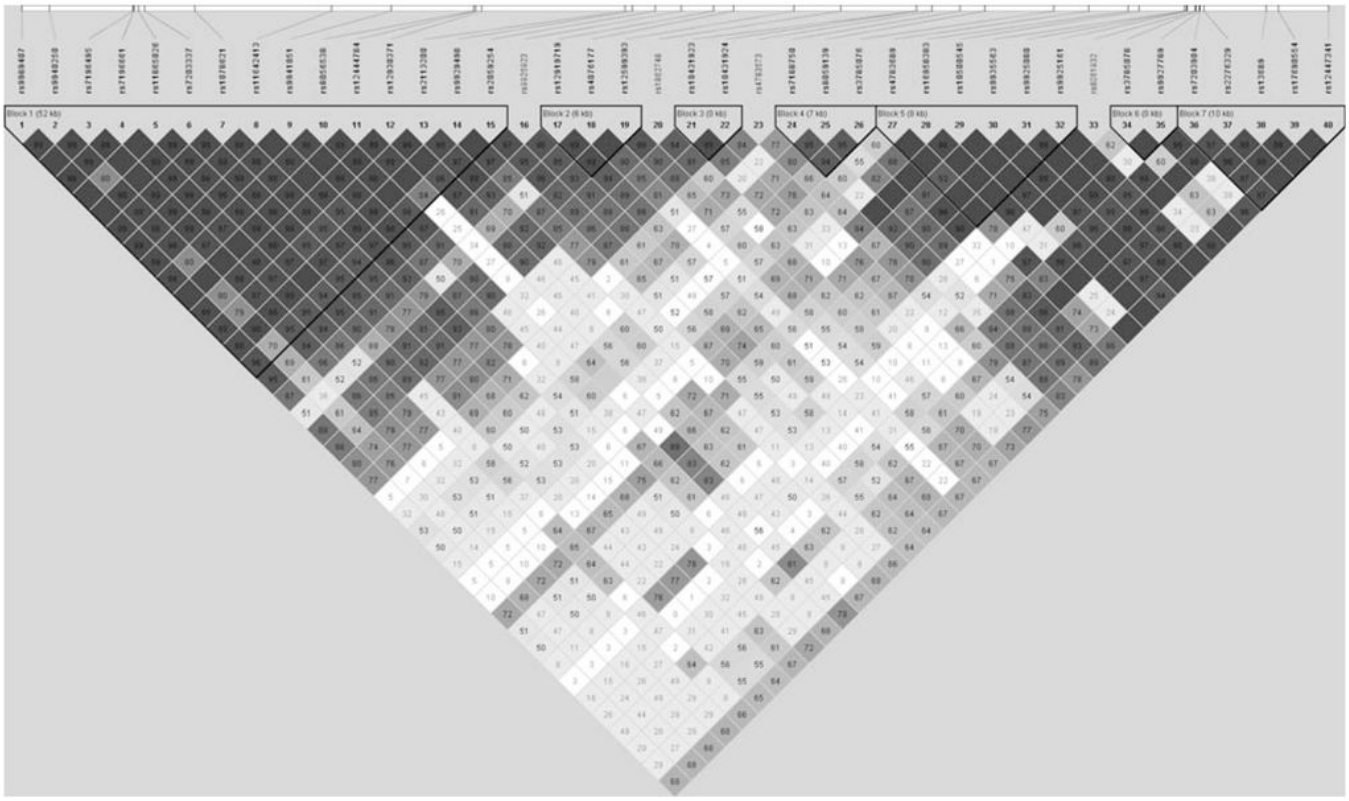

Fig. 1.
Linkage disequilibrium (LD) structure of 40 *E-cadherin* polymorphisms among 2,151 controls from the Shanghai Breast Cancer Study, value shown is D′

Table 1

Shanghai Breast Cancer Study participants genotyped for *E-cadherin*, the Shanghai Breast Cancer Study

Characteristics	Phase 1 (*N* = 2,290)			Phase 2 (*N* = 1,944)		
	Cases (*N* = 1,114)	Controls (*N* = 1,176)	*P* value	Cases (*N* = 969)	Controls (*N* = 975)	*P* value
Demographic factors						
Age (years)	47.6 ± 8.0	47.6 ± 8.3	0.807	51.4 ± 8.3	51.4 ± 8.2	0.913
Education (less than middle school)	138 (12.4%)	171 (14.5%)	0.132	69 (7.1%)	115 (11.8%)	< 0.001
Reproductive risk factors						
Age at menarche (years)	14.5 ± 1.6	14.7 ± 1.7	< **0.001**	14.5 ± 1.7	14.7 ± 1.8	**0.004**
Premenopausal	742 (67.0%)	704 (63.3%)	0.071	528 (54.5%)	516 (52.9%)	0.489
Age at menopause (years)[a]	48.1 ± 4.7	47.4 ± 5.0	**0.034**	48.7 ± 4.4	48.0 ± 4.5	**0.027**
Age at first live birth (years)[b]	26.8 ± 4.1	26.3 ± 3.8	**0.001**	26.1 ± 3.7	25.7 ± 3.8	**0.027**
Used oral contraceptives	244 (22.0%)	253 (21.6%)	0.811	175 (18.1%)	180 (18.5%)	0.819
Used estrogen replacement therapy	28 (2.5%)	30 (2.6%)	0.963	37 (3.8%)	21 (2.2%)	0.031
Additional risk factors						
First degree relative with breast cancer	37 (3.3%)	30 (2.6%)	0.272	55 (5.7%)	33 (3.4%)	**0.015**
Ever had breast fibroadenomas	105 (9.5%)	58 (5.0%)	< **0.001**	96 (10.0%)	63 (6.5%)	**0.005**
Body mass index (kg/m^2)	23.6 ± 3.4	23.2 ± 3.4	**0.013**	24.0 ± 3.3	23.4 ± 3.3	< **0.001**
Waist-to-hip ratio	0.81 ± 0.06	0.80 ± 0.06	**0.002**	0.84 ± 0.05	0.82 ± 0.06	< **0.001**
Regular physical activity	213 (19.2%)	300 (25.6%)	< **0.001**	308 (31.8%)	338 (34.7%)	0.178

Continuous variables: mean values ± standard deviation, *P* value from *t*-tests; Categorical variables: numbers and percentages, *P* values from χ^2 test

[a] Among postmenopausal women

[b] Among parous women

Bold values considered to be significant $P \leq 0.05$

Table 2

E-cadherin SNPs and breast cancer risk among all women, premenopausal women, and postmenopausal women, the Shanghai Breast Cancer Study

SNP	Alleles[a]	Region	Genotyping[b]	MAF[c]	HWE[d]	All women		Premenopausal women[f]		Postmenopausal women[g]	
						B OR (95% CI)[e]	*P* value[e]	B OR (95% CI)[e]	*P* value[e]	B OR (95% CI)[e]	*P* value
rs9989407	T/C	Promoter	Affy 6.0	25.8	0.560	1.1 (1.0–1.2)	0.334	1.0 (0.9–1.1)	0.673	**1.2 (1.0–1.4)**	**0.045**
rs9940250	T/C	Promoter	Targeted	27.9	0.905	1.0 (0.8–1.1)	0.594	0.9 (0.8–1.1)	0.427	1.0 (0.8–1.3)	0.849
rs7196495	T/C	Intron 2	Affy 6.0	25.9	0.630	1.0 (0.9–1.1)	0.409	1.0 (0.9–1.1)	0.635	1.2 (1.0–1.3)	0.065
rs7196661	T/C	Intron 2	Affy 6.0	25.9	0.630	1.0 (0.9–1.1)	0.416	1.0 (0.9–1.1)	0.637	1.2 (1.0–1.3)	0.069
rs11865026	T/C	Intron 2	Affy 6.0	24.2	0.976	1.0 (0.9–1.1)	0.671	1.0 (0.9–1.2)	0.627	0.9 (0.8–1.1)	0.216
rs7203337	G/C	Intron 2	Affy 6.0	49.8	0.630	1.0 (0.9–1.1)	0.724	1.0 (0.9–1.1)	0.999	1.0 (0.8–1.1)	0.569
rs1078621	C/T	Intron 2	Affy 6.0	49.2	0.155	1.0 (0.9–1.1)	0.449	1.0 (0.9–1.1)	0.923	0.9 (0.8–1.0)	0.177
rs11642413	G/A	Intron 2	Targeted	48.4	0.803	1.0 (0.9–1.2)	0.658	1.0 (0.9–1.2)	0.697	1.0 (0.8–1.3)	0.856
rs9941051	T/C	Intron 2	Affy 6.0	25.7	0.423	1.0 (0.9–1.1)	0.428	1.0 (0.9–1.1)	0.712	1.1 (1.0–1.3)	0.097
rs8056538	G/A	Intron 2	Affy 6.0	24.1	0.804	1.0 (0.9–1.1)	0.949	1.1 (0.9–1.2)	0.417	0.9 (0.8–1.1)	0.280
rs12444784	A/G	Intron 2	Both	8.2	0.069	0.9 (0.8–1.1)	0.352	0.8 (0.7–1.0)	0.058	1.1 (0.9–1.5)	0.342
rs12930371	C/T	Intron 2	Affy 6.0	24.1	0.548	1.0 (0.9–1.1)	0.966	1.1 (0.9–1.2)	0.308	0.9 (0.8–1.1)	0.283
rs2113200	T/A	Intron 2	Affy 6.0	24.5	0.864	1.0 (0.9–1.1)	0.723	1.0 (0.9–1.2)	0.554	0.9 (0.8–1.1)	0.203
rs9929498	G/A	Intron 2	Targeted	26.4	0.729	1.0 (0.9–1.1)	0.841	1.0 (0.8–1.1)	0.686	1.0 (0.8–1.3)	0.918
rs2059254	C/T	Intron 2	Both	16.6	0.469	1.0 (0.9–1.2)	0.690	**1.2 (1.0–1.4)**	**0.029**	**0.8 (0.7–1.0)**	**0.049**
rs9925923	C/T	Intron 2	Affy 6.0	17.1	0.578	1.0 (0.9–1.2)	0.678	**1.2 (1.0–1.4)**	**0.024**	**0.8 (0.7–1.0)**	**0.049**
rs12919719	C/G	Intron 2	Both	17.6	0.792	1.0 (0.9–1.1)	0.913	1.2 (1.0–1.4)	0.057	**0.8 (0.7–1.0)**	**0.044**
rs4076177	A/G	Intron 2	Targeted	20.8	0.668	1.1 (0.9–1.2)	0.508	1.1 (0.9–1.3)	0.307	**1.0 (0.8–1.3)**	0.904
rs12599393	C/T	Intron 2	Affy 6.0	17.1	0.638	1.0 (0.9–1.1)	0.752	1.1 (1.0–1.3)	0.129	**0.8 (0.7–1.0)**	**0.020**
rs1862748	C/T	Intron 2	Both	18.1	0.707	1.0 (0.9–1.1)	0.834	1.1 (1.0–1.3)	0.100	**0.8 (0.7–1.0)**	**0.027**
rs10431923	T/G	Intron 2	Affy 6.0	45.2	0.311	1.0 (1.0–1.2)	0.424	1.1 (1.0–1.2)	0.222	1.0 (0.9–1.1)	0.875
rs10431924	C/T	Intron 2	Targeted	44.7	0.735	1.0 (0.9–1.2)	0.631	1.1 (0.9–1.2)	0.355	1.0 (0.8–1.2)	0.703
rs4783573	G/A	Intron 2	Both	21.9	0.370	1.0 (0.9–1.1)	0.545	1.0 (0.9–1.2)	0.598	1.0 (0.9–1.2)	0.707
rs7188750	G/A	Intron 5	Both	18.5	0.226	1.0 (0.9–1.2)	0.573	0.9 (0.8–1.1)	0.354	1.2 (1.0–1.4)	0.052
rs8059139	A/G	Intron 6	Both	11.1	0.326	1.0 (0.9–1.2)	0.758	1.0 (0.8–1.2)	0.627	1.1 (0.9–1.4)	0.339
rs3785076	A/G	Intron 10	Targeted	11.7	0.327	1.0 (0.8–1.2)	0.895	1.1 (0.8–1.3)	0.684	0.9 (0.7–1.3)	0.636
rs4783689	C/T	Intron 11	Both	32.9	0.250	1.0 (1.0–1.1)	0.372	1.1 (1.0–1.2)	0.134	1.0 (0.8–1.1)	0.668
rs16958383	G/A	Intron 12	Targeted	20.7	0.542	1.0 (0.8–1.1)	0.514	**0.8 (0.7–1.0)**	**0.020**	1.3 (1.0–1.7)	0.062

SNP	Alleles[a]	Region	Genotyping[b]	MAF[c]	HWE[d]	All women		Premenopausal women[f]		Postmenopausal women[g]	
						B OR (95% CI)[e]	*P* value[e]	B OR (95% CI)[e]	*P* value[e]	B OR (95% CI)[e]	*P* value
rs10500545	A/T	Intron 13	Targeted	12.6	0.989	1.0 (0.8–1.2)	0.692	0.9 (0.7–1.1)	0.194	1.1 (0.8–1.5)	0.415
rs9935563	C/T	Intron 13	Targeted	35.7	0.620	1.0 (0.9–1.1)	0.690	1.1 (0.9–1.3)	0.213	**0.8 (0.6–1.0)**	**0.041**
rs9925080	G/A	Intron 13	Affy 6.0	9.3	0.182	1.0 (0.9–1.1)	0.724	0.9 (0.7–1.1)	0.281	1.1 (0.9–1.4)	0.519
rs9925161	G/A	Intron 13	Both	9.3	0.111	1.0 (0.9–1.1)	0.879	0.9 (0.7–1.1)	0.304	1.1 (0.9–1.4)	0.377
rs8061932	T/C	Intron 14	Both	22.8	0.855	1.0 (0.9–1.1)	0.623	0.9 (0.8–1.0)	0.073	1.1 (1.0–1.3)	0.176
rs3785078	A/C	Intron 14	Targeted	13.7	0.585	0.9 (0.8–1.1)	0.465	0.9 (0.7–1.1)	0.223	1.1 (0.8–1.5)	0.634
rs9927789	A/C	Intron 14	Targeted	19.0	0.214	1.0 (0.9–1.2)	0.888	0.9 (0.8–1.1)	0.565	1.1 (0.9–1.5)	0.396
rs7203904	G/C	Intron 14	Targeted	32.5	0.706	1.0 (0.9–1.1)	0.896	0.9 (0.8–1.0)	0.128	1.2 (1.0–1.5)	0.098
rs2276329	T/C	Intron 14	Both	9.7	0.257	1.0 (0.9–1.2)	0.952	0.9 (0.8–1.1)	0.582	1.1 (0.9–1.3)	0.511
rs13689	T/C	3′ UTR	Affy 6.0	19.0	0.397	1.0 (0.9–1.1)	0.760	0.9 (0.8–1.1)	0.220	1.2 (1.0–1.4)	0.062
rs17690554	C/G	3′ FR[h]	Affy 6.0	19.1	0.399	1.0 (0.9–1.2)	0.834	0.9 (0.8–1.1)	0.214	1.2 (1.0–1.4)	0.082
rs12447341	C/T	3′ FR[h]	Targeted	29.0	0.698	1.0 (0.9–1.1)	0.507	1.1 (0.9–1.3)	0.474	0.8 (0.6–1.0)	0.057

[a] Major/minor alleles as determined by allele frequency among genotyped controls

[b] Genotyping and study phase: Affymetrix targeted genotyping among 1,062 cases and 1,069 controls from phase 1 (Targeted), or Affymetrix 6.0 genotyping among 1,104 cases and 1,109 controls from Phase 1 and 969 cases and 975 controls from phase 2 (Affy 6.0), or genotyped by both (Both)

[c] Minor allele freqency among genotyped controls

[d] Hardy–Weinberg equilibrium test among controls

[e] Risk of breast cancer per minor allele, adjusted for age, education, and study phase (when appropriate); *A* major allele, *B* minor allele; *P* value for trend

[f] Premenopausal Women: 717 cases and 692 controls from phase 1 (Targeted), or 745 caes and 758 controls from phase 1 and 528 cases and 516 controls from phase 2 (Affy 6.0)

[g] Postmenopausal Women: 345 cases and 377 controls from phase 1 (Targeted), or 369 caes and 419 controls from phase 1 and 441 cases and 459 controls from phase 2 (Affy 6.0)

[h] 3′ FR: 3′ flanking region, downstream of the *CDH1* gene

Bold values considered to be significant $P \leq 0.05$

Table 3

Selected *E-cadherin* SNPs and breast cancer risk, by menopausal status and study phase, the Shanghai Breast Cancer Study

SNP	Alleles[a]	Region	Model[b]	Premenopausal women[c]					
				Phase 1		Phase 2		Combined	
				OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
rs9989407	T/C	Promoter	R	0.8 (0.5–1.2)	0.286	1.1 (0.7–1.9)	0.715	0.9 (0.7–1.3)	0.576
rs7196495	T/C	Intron 2	R	0.8 (0.5–1.2)	0.285	1.1 (0.7–1.9)	0.630	0.9 (0.7–1.3)	0.625
rs7196661	T/C	Intron 2	R	0.8 (0.6–1.2)	0.345	1.1 (0.7–1.8)	0.731	0.9 (0.7–1.3)	0.636
rs9941051	T/C	Intron 2	R	0.8 (0.5–1.2)	0.280	1.1 (0.7–1.9)	0.630	0.9 (0.7–1.3)	0.629
rs2059254	C/T	Intron 2	D	1.2 (1.0–1.6)	0.073	1.3 (1.0–1.7)	0.055	**1.3 (1.1–1.5)**	**0.009**
rs9925923	C/T	Intron 2	D	**1.3 (l.0–1.6)**	**0.044**	1.3 (1.0–1.7)	0.053	**1.3 (1.1–1.5)**	**0.006**
rs12919719	C/G	Intron 2	D	1.2 (0.9–1.5)	0.133	1.3 (1.0–1.6)	0.091	**1.2 (1.0–1.5)**	**0.027**
rs12599393	C/T	Intron 2	D	1.2 (0.9–1.5)	0.179	1.2 (0.9–1.5)	0.211	1.2 (1.0–1.4)	0.073
rs1862748	C/T	Intron 2	D	1.2 (0.9–1.5)	0.206	1.2 (0.9–1.5)	0.215	1.2 (1.0–1.4)	0.080
rs7188750	G/A	Intron 5	R	**0.4 (0.2–0.9)**	**0.014**	0.8 (0.4–1.5)	0.427	**0.6 (0.4–0.9)**	**0.019**
rs13689	T/C	3′ UTR	R	0.7 (0.4–1.1)	0.143	0.7 (0.4–1.4)	0.362	0.7 (0.5–1.1)	0.086
rs17690554	C/G	3′ FR[e]	R	0.7 (0.4–1.1)	0.142	0.7 (0.4–1.4)	0.362	0.7 (0.5–1.1)	0.085

SNP	Alleles[a]	Region	Model[b]	Postmenopausal women[d]					
				Phase 1		Phase 2		Combined	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
rs9989407	T/C	Promoter	R	**1.8 (1.0–3.2)**	**0.041**	1.3 (0.8–2.2)	0.272	**1.5 (1.0–2.2)**	0.031
rs7196495	T/C	Intron 2	R	**1.8 (1.0–3.2)**	**0.038**	1.3 (0.8–2.2)	0.305	**1.5 (1.0–2.2)**	0.034
rs7196661	T/C	Intron 2	R	**1.8 (1.0–3.2)**	**0.037**	1.3 (0.8–2.2)	0.313	**1.5 (1.0–2.2)**	0.035
rs9941051	T/C	Intron 2	R	**1.8 (1.0–3.2)**	**0.045**	1.3 (0.8–2.1)	0.362	1.5 (1.0–2.1)	0.052
rs2059254	C/T	Intron 2	D	0.9 (0.6–1.3)	0.536	**0.7 (0.5–1.0)**	**0.026**	**0.8 (0.6–1.0)**	**0.032**
rs9925923	C/T	Intron 2	D	0.9 (0.6–1.2)	0.393	**0.7 (0.6–1.0)**	**0.049**	**0.8 (0.6–1.0)**	**0.034**
rs12919719	C/G	Intron 2	D	0.9 (0.6–1.2)	0.439	**0.7 (0.5–1.0)**	**0.029**	**0.8 (0.6–1.0)**	**0.025**
rs12599393	C/T	Intron 2	D	0.9 (0.6–1.2)	0.340	**0.7 (0.5–1.0)**	**0.031**	**0.8 (0.6–1.0)**	**0.016**
rs1862748	C/T	Intron 2	D	0.9 (0.6–1.2)	0.376	**0.7 (0.5–0.9)**	**0.019**	**0.8 (0.6–0.9)**	**0.014**

SNP	Alleles[a]	Region	Model[b]	Postmenopausal women[d]					
				Phase 1		Phase 2		Combined	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
rs7188750	G/A	Intron 5	R	1.6 (0.7–3.7)	0.256	1.6(0.8–3.0)	0.195	1.6 (1.0–2.7)	0.070
rs13689	T/C	3′ UTR	R	1.6 (0.8–3.2)	0.183	1.7 (0.8–3.4)	0.158	**1.7 (1.0–2.7)**	**0.043**
rs17690554	C/G	3′ FR[e]	R	1.5 (0.8–3.0)	0.234	1.7 (0.8–3.4)	0.158	1.6 (1.0–2.6)	0.059

[a] Major/minor alleles as determined by allele frequency among genotyped controls

[b] Model of effect: dominant (D): AB and BB versus AA, or recessive (R): BB versus AA and AB; *AA* major allele homozygotes, *AB* heterozygotes, *BB* minor allele homozygotes

[c] Risk of breast cancer, adjusted for age and education for premenopausal women; Phase 1 includes 745 cases and 758 controls, Phase 2 includes 528 cases and 516 controls

[d] Risk of breast cancer, adjusted for age and education for postmenopausal women; Phase 1 includes 369 cases and 419 controls, Phase 2 includes 441 cases and 459 controls

[e] 3′ FR: 3′ flanking region, downstream of the *CDH1* gene

Bold values considered to be significant $P \leq 0.05$