Polymorphisms in Steroid Hormone Biosynthesis Genes and Risk of Breast Cancer and Fibrocystic Breast Conditions in Chinese Women

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Abstract

Common variants in genes encoding for key enzymes involved in steroidogenesis may alter sex steroid hormone levels, thereby influencing susceptibility to breast carcinoma and related conditions. In a case-control study of Chinese women, we examined genotypes of the *CYP11A1* pentanucleotide [$(TAAAA)_n$] repeat (D15S520), *CYP17A1* rs743572, and *HSD17B1* rs605059 polymorphisms in relation to the risk of breast cancer and fibrocystic breast conditions, comparing 615 women with breast cancer and 467 women with fibrocystic breast conditions separately with 879 women without clinical breast disease. We also evaluated whether these relationships differed by the presence of proliferation in the extratumoral epithelium or fibrocystic lesions, menopausal status, or body mass index. Only *CYP11A1* genotype was related to breast cancer risk, with women homozygous for the 4-repeat allele, relative to those homozygous for the 6-repeat allele, at reduced risk (age-adjusted odds ratio, 0.58; 95% confidence interval, 0.37-0.91). There was some suggestion of a stronger inverse association for breast cancer with evidence of proliferation in the extratumoral epithelium than for breast cancer without extratumoral proliferation. Breast cancer risk associated with *CYP11A1* genotype did not differ by menopausal status or body mass index level. No associations between *CYP11A1*, *CYP17A1*, and *HSD17B1* genotypes and risk of fibrocystic breast conditions were observed. Our findings support the possibility that common allelic variation at the *CYP11A1* D15S520 locus alters breast cancer risk in Chinese women. (Cancer Epidemiol Biomarkers Prev 2008;17(5):1066–73)

Introduction

Risk of breast cancer has been associated with higher levels of endogenous estrogens and androgens (1, 2). Biosynthesis of these steroid hormones involves a series of enzymatic reactions, with the first catalyzed by the cholesterol side-chain cleavage (*P*450scc) enzyme, encoded by the *CYP11A1* gene, which converts cholesterol to pregnenolone (3). Other key reactions include the conversion of pregnenolone and progesterone to dehydroepiandrosterone and androstenedione, catalyzed by the *CYP17A1* gene-encoded cytochrome *P*450c17α enzyme, and the conversion of estrone to the more biologically active estradiol, catalyzed by the *HSD17B1* gene-encoded 17β-hydroxysteroid dehydrogenase type 1 enzyme. Polymorphisms in steroid hormone biosynthesis genes, such as *CYP11A1*, *CYP17A1*, and *HSD17B1*, could result in altered levels of sex steroid hormones and thereby influence the development of breast cancer.

The few epidemiologic studies examining *CYP11A1* variation (4-6) provide some evidence to support this hypothesis. Of particular interest has been a pentanucleotide repeat $(TAAAA)_n$ polymorphism (D15S520), positioned 528 bp upstream of the translational start site (7), in the gene promoter. In a study conducted in Shanghai, carriage of at least one (versus no) copy of the eight TAAAA repeat allele was first reported to confer a 60% increase in breast cancer risk (4), and a more comprehensive examination has since revealed breast cancer risk may be additionally related to other variants located upstream of the coding region (5). Modest associations between *CYP11A1* haplotypes and breast cancer risk have also been noted in the Multiethnic Cohort Study population (6).

The relationship between a T (A1 allele) and a C (A2 allele) base substitution at position +27 from the transcription start site (or -34 from the translation start site) in the 5′-untranslated region of the *CYP17A1* gene (rs743572), which creates another Sp-1-type (CCACC box) promoter motif between translation and transcription start sites (8), and breast cancer risk is not entirely clear. Although most studies have found no overall

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relationship (9, 10), some studies of non-Caucasian women have found breast cancer risk associated with this polymorphism to vary by age or menopausal status (11-14), body mass index (BMI; ref. 13), and age at first birth and parity combined (15). Furthermore, although *in vitro* data have not confirmed that the additional Sp-1 binding site leads to increased gene transcription (16), higher endogenous levels of estrogens and androgens have been reported in carriers (versus noncarriers) of the A2 allele (17).

The results from studies of *HSD17B1* variation examining a single nucleotide polymorphism in exon 6 (rs605059), known to produce an amino acid change from serine to glycine at position 312, are also somewhat inconsistent (15, 18-21). In a study conducted in Singapore, a 1.8-fold increased risk of breast cancer was found for postmenopausal Chinese women with the AA genotype (15). However, in a pooled analysis of 5,370 cases and 7,480 matched controls from the Breast and Prostate Cancer Cohort Consortium, the majority of whom were Caucasian, none of the common *HSD17B1* haplotypes defined by four haplotype-tagging single nucleotide polymorphisms (including rs605059) were associated with breast cancer risk (21). Although the results of the earlier study may be due to chance, the association could also differ by race.

Inconsistent results between genetic susceptibility studies of breast cancer conducted in different ethnic populations may be explained by population differences in the allele frequencies of common polymorphisms and the prevalence of known risk factors for breast cancer. The most frequent alleles of the *CYP11A1* D15S520 and *CYP17A1* rs743572 polymorphisms, respectively, are the 4-repeat and A1 alleles among Caucasians but the 6-repeat and A2 allele among Asians (17, 22). The prevalence of exogenous hormone use and obesity is much higher among women residing in western countries than in China (23, 24). Therefore, modest associations between polymorphisms in steroid hormone biosynthesis genes and breast cancer risk may be easier to detect in Chinese women who tend to have lower circulating estrogen levels.

A woman's risk for fibrocystic breast conditions may be similarly influenced by polymorphisms in steroid hormone biosynthesis genes. To our knowledge, this hypothesis has not been tested. Because women who develop proliferative breast lesions tend to have a greater risk of breast cancer compared with women who develop nonproliferative breast lesions (25-28), discovering genetic markers associated with fibrocystic breast changes, especially those that are proliferative, could help to further characterize women who are most likely to develop breast cancer.

In a case-control study of Chinese women enrolled in a randomized trial of breast self-examination, we investigated whether the aforementioned *CYP11A1, CYP17A1*, and *HSD17B1* polymorphisms were associated with risk of breast cancer and fibrocystic breast conditions. We also examined whether these associations differed according to the presence of proliferation in nonmalignant tissue (surrounding the tumor or from the fibrocystic lesion), menopausal status, and BMI. Menopausal status and BMI were secondarily evaluated as potential effect modifiers, because adrenal androgens are converted into biologically active estrogens in adipose tissue, which is the main source of endogenous estrogens in postmenopausal women.

Materials and Methods

Study Population. Participants in this case-control study were drawn from a randomized trial examining the effect of regular breast self-examination on breast cancer mortality in Shanghai, China. Details of this trial have been published (29, 30). Briefly, from October 1989 to October 1991, the trial enrolled 266,064 women, born between 1925 and 1958, who were current or retired employees of the Shanghai Textile Industry Bureau. At enrollment, each participant was interviewed by a trained factory medical worker. Follow-up of each participant was conducted on vital status, continued employment in the textile industry, residence in Shanghai, and occurrence of benign or malignant breast conditions until July 31, 2000.

As reported in detail previously (31), the present study was composed of women who were reinterviewed and had their blood drawn for several case-control studies of benign and malignant breast conditions conducted from September 1995 to July 2000. Cases were women who had a breast biopsy and were subsequently diagnosed as having a fibrocystic breast condition between September 1995 and July 2000 or breast cancer between November 1989 and July 2000. Controls were a random sample of women in the cohort who did not have a breast biopsy. Two controls were selected for each case diagnosed between September 1995 and August 1997 by matching on age and menstrual status, but this matching was not retained in the analysis. Controls were frequency matched to the remaining cases on age (in 5-year age groups) and hospital affiliation of their factories at baseline. This study included 615 women with breast cancer, 467 women with fibrocystic breast conditions, and 879 controls, after excluding 43 women (8 with breast cancer, 3 with fibrocystic breast conditions, and 32 controls) based on evidence of sample contamination, indicated by discrepant genotyping results of DNA from paired buffy coat and whole-blood aliquot samples.

At the time of interview, information on demographic characteristics, reproductive and gynecologic history, smoking and alcohol use, medical history, family history of breast cancer, occupational and recreational physical activity, and usual diet was collected by questionnaire. Measurements of height and weight were also recorded.

All women provided informed consent before interview. The study protocol was approved by the Institutional Review Office of the Fred Hutchinson Cancer Research Center, the Station for Prevention and Treatment of Cancer of the Shanghai Textile Industry Bureau in accordance with an assurance filed with the Office for Human Research Protections of the U.S. Department of Health and Human Services, and the Human Genetic Resources Administration Office of China.

Histologic Classification of Breast Tissue. A single pathologist who was unaware of the original diagnoses provided an independent histologic diagnosis of all cases of benign and malignant breast conditions. In addition, for cases diagnosed after September 1995, benign changes, either in the fibrocystic lesion in women with

benign conditions or in the extratumoral epithelium in women with breast cancer, were further classified by this pathologist as nonproliferative or proliferative when sufficient mammary gland tissue (excluding areas of fibroadenoma) was available for microscopic review with at least five scanning power fields. Sufficient tissue was available for 337 (72%) of the 467 women with fibrocystic conditions and 241 (75%) of the 320 women with breast cancer diagnosed after September 1995.

Classification followed a scheme developed by Stalsberg (32), which is similar to Page's classification for benign breast disease (25). Women with atypical ductal hyperplasia, atypical lobular hyperplasia, or moderate apocrine atypia were classified as having atypia. Women with moderate or florid ductal hyperplasia or with moderate or predominant sclerosing adenosis and no atypia were classified as having proliferative changes without atypia. Women with mild or no ductal hyperplasia and with mild or no sclerosing adenosis were classified as having nonproliferative changes.

A detailed description of the procedures implemented to assure reliability of our histologic classification has been published previously (33). Briefly, the pathologist who conducted the histologic review was trained by Stalsberg, who also read study samples of various fibrocystic breast conditions and of nonmalignant epithelial tissue adjacent to breast tumors. Agreement between the two pathologists on the extent of proliferation and presence of atypia was satisfactory (weighted $\kappa = 0.4$).

Genotyping. Genomic DNA was isolated from buffy coat using a salt precipitation (34) and/or a phenol-chloroform method (35, 36). When the quantity of DNA from buffy coat was insufficient for genotyping, genomic DNA was isolated from a whole blood sample corresponding to the same subject using the QIAamp DNA Blood Midi Kit (Qiagen). Genomic DNA was also extracted from whole blood for subjects in the rare instances when the genotyping results using DNA from buffy coat for a set of microsatellite polymorphisms (including the *CYP11A1* pentanucleotide repeat) suggested possible sample contamination.

CYP11A1. The *CYP11A1* $(TTTTA)_n$ repeat was amplified using the primers described by Gharani et al. (7): FAM-labeled forward primer: 5′-AGGTGAAACTGTGC-CATTGC-FAM and reverse primer: 5′-GTTTGG-GGGAAATGAGGGG. The amplified fragment ranged from 211 to 250 bp in length (4-12 repeats). A 20 μL reaction consisted of 25 ng genomic DNA, 150 nmol/L of each primer, Taq PCR Master Mix, and 200 μmol/L of each deoxynucleotide triphosphate (Qiagen). Amplifications were done in a GeneAmp PCR System 9700 (Applied Biosystems) as follows: initial denaturation at 95°C for 2 min; 10 cycles of 94°C for 45 s, 62°C for 30 s, and 72°C for 1 min followed by 25 cycles of 94°C for 45 s, 60°C for 30 s, and 72°C for 1 min; and a final extension of 72°C for 5 min. The products were mixed with HiDi formamide (Applied Biosystems) and GeneScan-500 LIZ Size Standard (Applied Biosystems) and electrophoresed on an ABI Prism 3100 Genetic Analyzer. Resulting data were analyzed using ABI GeneScan 3.7 and GeneMapper 2.0 genotyping software.

CYP17A1. Genotypes for the *CYP17A1* 5′-untranslated region *Msp*I T→C polymorphism (rs743572) were determined essentially according to Carey et al. (8).

HSD17B1. SNaPshot (Applied Biosystems) assays were used to determine genotype for the *HSD17B1* S312G polymorphism (rs605059). A 10 μL reaction contained 30 ng genomic DNA, 1× Taq PCR Master Mix, 200 μmol/L of each deoxynucleotide triphosphate (Qiagen), and 200 nmol/L of each forward (5′-CCTGCGCTACTTCACCACC) and reverse (5′-CCAC-CCACAGCTGCTACC) primers. Thermal cycling done in a GeneAmp PCR System 9700 (Applied Biosystems) involved initial denaturation at 94°C for 5 min followed by 40 cycles of 94°C for 1 min, 56°C for 1 min, and 72°C for 2 min with a final extension of 72°C for 5 min. Products were purified with a SAP/*Exo*I (SAP: Amersham/Pharmacia; *Exo*I: New England Biolabs) treatment to remove unincorporated deoxynucleotide triphosphates/primers, respectively, according to the ABI Prism SNaPshot Multiplex Kit instructions. Thermal cycling was also conducted according to the SNaPshot Kit using a GeneAmp PCR System 9700 (Applied Biosystems) and *HSD17B1* SNaPshot primer [5′-$(GACT)_{17}$GGGTCCCC-CACCGCAC]. After thermal cycling and removal of unincorporated [F]dideoxynucleotide triphosphates, the products were mixed with HiDi formamide (Applied Biosystems) and GeneScan-120 LIZ Size Standard (Applied Biosystems) and electrophoresed on an ABI Prism 3100 Genetic Analyzer. Resulting data were analyzed using ABI GeneScan 3.7 and GeneMapper 2.0 genotyping software.

Quality Control. Similar quality-control procedures were implemented for each assay. Three in-house genomic DNA samples of known genotype were included as positive controls and a reaction without DNA template was included as a negative control in every batch of 92 samples. The same set of positive controls was run in every batch for a given assay. For the *CYP11A1* assay, the positive controls were representative clones with confirmed sequences of four, six, and eight TTTTA repeats. For the *CYP17A1* and *HSD17B1* assays, the positive controls included a homozygote for the major allele, a heterozygote, and a homozygote for the minor allele. Laboratory personnel were blinded to the case-control status of the samples.

Statistical Analysis. Age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression to assess the risks of breast cancer and fibrocystic breast conditions associated with each polymorphism. For the *CYP11A1* $(TTTTA)_n$ polymorphism, risk estimates were calculated for each genotype with an observed frequency of >1% relative to the homozygous genotype of the most common allele (6-repeat allele). Genotypes with an observed frequency of <1% were combined into a single category in the analysis. Risk estimates were also calculated for carriage of the 4-, 6-, and 8-repeat allele, with no copies of a given allele selected as the reference group, permitting the comparison of results from a prior study (4) and ours. The reference groups for the *CYP17A1* and *HSD17B1* polymorphisms were homozygous carriers of the A1 allele and homozygous carriers of the G allele, respectively.

Among the subset of women with sufficient tissue available for histologic classification of nonmalignant tissue, analyses stratified according to proliferation status were conducted. Proliferation status was

Table 1. Selected characteristics and allele frequencies for controls and cases of breast cancer and fibrocystic breast conditions

	Controls, *n* (%)	Breast cancer, *n* (%)			Fibrocystic breast conditions, *n* (%)		
		Overall	Nonproliferative	Proliferative	Overall	Nonproliferative	Proliferative
Characteristics							
Age (y)							
<40	12 (1.4)	78 (12.7)	3 (2.4)	5 (0.2)	62 (13.3)	22 (14.3)	20 (10.9)
40-44	376 (42.8)	169 (27.5)	35 (28.0)	32 (27.6)	200 (42.8)	62 (40.2)	81 (44.3)
45-49	171 (19.5)	97 (15.8)	26 (20.8)	30 (25.9)	123 (26.3)	42 (27.3)	50 (27.3)
50-54	64 (7.3)	40 (6.5)	13 (10.4)	9 (7.8)	22 (4.7)	11 (7.1)	6 (3.3)
55-59	38 (4.3)	47 (7.6)	9 (7.2)	3 (2.6)	12 (2.6)	5 (3.2)	2 (1.1)
60-64	106 (12.1)	99 (16.1)	18 (14.4)	17 (14.7)	15 (3.2)	2 (1.3)	10 (5.5)
≥65	112 (12.7)	85 (13.8)	21 (16.8)	20 (17.2)	33 (7.1)	10 (6.5)	14 (7.6)
Age at menopause (y)							
Premenopausal	529 (60.2)	294 (53.1)	60 (59.7)	68 (64.9)	375 (64.3)	127 (65.1)	143 (63.1)
<45	61 (6.9)	64 (10.9)	13 (9.0)	5 (3.3)	20 (5.6)	5 (7.9)	7 (3.9)
45-49	127 (14.5)	117 (17.7)	20 (12.6)	21 (15.3)	35 (12.7)	8 (8.3)	17 (14.5)
≥50	162 (18.4)	140 (18.3)	32 (18.7)	22 (16.5)	37 (17.4)	14 (18.7)	16 (18.5)
BMI (kg/m^2)							
<20.0	158 (18.0)	92 (14.2)	18 (15.7)	43 (19.1)	158 (18.8)	22 (22.4)	39 (16.2)
20.1-25.0	518 (58.9)	356 (58.4)	75 (60.3)	89 (58.0)	518 (58.4)	64 (53.4)	109 (60.5)
>25.0	203 (23.1)	165 (27.4)	32 (24.0)	22 (22.8)	203 (22.8)	29 (24.2)	34 (23.3)
Allele frequency							
CYP11A1 D15S520							
4	451 (25.7)	278 (22.6)	59 (23.6)	46 (19.8)	229 (24.6)	73 (23.9)	100 (27.3)
6	1,070 (61.0)	798 (65.0)	167 (66.8)	159 (68.5)	576 (61.9)	192 (62.7)	220 (60.1)
7	9 (0.5)	7 (0.6)	0 (0.0)	1 (0.4)	3 (0.3)	0 (0.0)	3 (0.8)
8	208 (11.9)	132 (10.7)	23 (9.2)	25 (10.8)	115 (12.4)	38 (12.4)	42 (11.5)
9	6 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)	2 (0.7)	0 (0.0)
10	4 (0.2)	9 (0.7)	1 (0.4)	0 (0.0)	2 (0.2)	1 (0.3)	0 (0.0)
11	4 (0.2)	1 (0.1)	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
12	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)
CYP17A1 rs743572							
A1	717 (40.9)	501 (40.7)	107 (42.8)	94 (40.5)	389 (41.6)	131 (42.5)	139 (38.0)
A2	1,037 (59.1)	729 (59.3)	143 (57.2)	138 (59.5)	545 (58.4)	177 (57.5)	227 (62.0)
HSD17B1 rs605059							
G	1,027 (58.8)	707 (57.6)	152 (60.8)	133 (52.2)	534 (57.4)	173 (56.5)	208 (56.8)
A	721 (41.2)	521 (42.4)	98 (39.2)	122 (47.8)	396 (42.6)	133 (43.5)	158 (43.2)

NOTE: For all characteristics, except age, the direct age-adjusted percentages based on the age distribution of controls are presented for cases of breast cancer and fibrocystic conditions.

categorized dichotomously into nonproliferative or proliferative for cases of breast cancer based on the absence or presence of proliferation in the nonmalignant epithelium surrounding the tumor and for cases of fibrocystic conditions based on the absence or presence of proliferation in the epithelium of the lesion(s). Proliferation was defined by either atypia or proliferative changes without atypia. Stratified analyses were also conducted to evaluate whether the association of each polymorphism with either outcome (breast cancer or fibrocystic breast conditions) differed by menopausal status (premenopausal, postmenopausal) or BMI level (≤20.0, 20.1-25.0, >25.0 kg/m^2). Statistical analyses were done using Stata 9 (StataCorp).

Results

Genotype frequencies among controls did not deviate from Hardy-Weinberg equilibrium. Genotyping success percentages for the *CYP11A1*, *CYP17A1*, and *HSD17B1* polymorphisms were 100% (1,956 of 1,956), 100% (1,959 of 1,959), and 99.8% (1,953 of 1,957), respectively; limited quantities of DNA precluded the genotyping of several women for all three polymorphisms. Across the 24 plates, genotype accuracy for the *CYP11A1* and *HSD17B1* polymorphisms was 100% for two positive controls and the negative control and 95.8% (23 of 24 genotype calls correct) for one positive control. For the *CYP17A1* polymorphism, genotype accuracy was 100% for all four controls.

Age-adjusted frequencies for age at menopause and BMI, along with allele frequencies of each polymorphism, by case-control and proliferation status are presented in Table 1. Frequency distributions for age at menopause and BMI were adjusted to the age distribution of controls, because the controls were younger than the cases. Relative to controls, cases with breast cancer were more likely to be postmenopausal and have a higher BMI, whereas cases with fibrocystic breast conditions were more likely to be premenopausal and have a similar BMI. For the *CYP11A1* D15S520 polymorphism, eight alleles were observed, containing 4, 6, 7, 8, 9, 10, 11, or 12 (TTTTA) repeats. The most common alleles with 4, 6, or 8 repeats accounted for >98% of the total alleles identified. Cases with breast cancer had a slightly higher frequency of the 6-repeat allele, but a slightly lower frequency of the 4-repeat allele, compared with both cases with fibrocystic breast conditions and controls. In contrast, *CYP17A1* and *HSD17B1* allele frequencies were similar in cases with

breast cancer, cases with fibrocystic breast conditions, and controls.

Age-adjusted risk estimates for breast cancer and fibrocystic breast conditions in relation to *CYP11A1, CYP17A1*, and *HSD17B1* genotype, overall and by proliferation status, are presented in Tables 2 and 3. With respect to the *CYP11A1* D15S520 polymorphism, an OR for breast cancer of 0.58 was observed for women homozygous for the 4-repeat allele, relative to women homozygous for the 6-repeat allele. This inverse relationship appeared to be stronger for breast cancer with concomitant proliferative changes in the extratumoral epithelium (OR, 0.34; 95% CI, 0.12-0.98). When *CYP11A1* genotype was defined in terms of carrier status for the 4-repeat allele, homozygous carriers of the allele relative to noncarriers were also at decreased breast cancer risk (OR, 0.61; 95% CI, 0.39-0.96). When *CYP11A1* genotype was defined in terms of carrier status for the 6-repeat allele, homozygous carriers of this allele relative to noncarriers were at increased breast cancer risk (OR, 1.42; 95% CI, 1.03-1.97). Carriage of one or two copies of the 8-repeat allele, however, was not associated with breast cancer risk. No associations between *CYP11A1* genotype and risk of fibrocystic breast conditions were found. *CYP17A1* and *HSD17B1* genotypes were not associated with altered risk of either breast cancer or fibrocystic breast conditions. Similar results were found when the prevalent cases of breast cancer were excluded from the analysis and when additional adjustment for menopausal status and BMI was done (data not shown).

The associations between *CYP11A1, CYP17A1*, and *HSD17B1* genotype and risk of breast cancer or fibrocystic breast conditions did not differ by menopausal status or BMI level, but for some comparisons, which were based on small numbers, the power to detect

Table 2. Age-adjusted OR (95% CI) for *CYP11A1* genotypes and risk of breast cancer and fibrocystic breast conditions, overall and by proliferation status of nontumor breast tissue

Genotype	Controls	Breast cancer						Fibrocystic breast conditions					
		Overall		Nonproliferative		Proliferative		Overall		Nonproliferative		Proliferative	
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
CYP11A1 D15S520													
6 repeat/6 repeat	330	260	1.00 (reference)	55	1.00 (reference)	56	1.00 (reference)	182	1.00 (reference)	64	1.00 (reference)	68	1.00 (reference)
6 repeat/4 repeat	259	179	0.88 (0.68-1.13)	37	0.85 (0.55-1.34)	30	0.68 (0.42-1.09)	142	1.04 (0.78-1.37)	47	0.96 (0.63-1.45)	60	1.17 (0.79-1.72)
4 repeat/4 repeat	68	31	0.58 (0.37-0.91)	9	0.81 (0.38-1.73)	4	0.34 (0.12-0.98)	25	0.67 (0.41-1.11)	5	0.39 (0.15-1.01)	13	0.93 (0.48-1.79)
4 repeat/8 repeat	48	31	0.82 (0.50-1.32)	3	0.36 (0.11-1.21)	7	0.85 (0.36-1.97)	33	1.34 (0.82-2.19)	14	1.66 (0.85-3.23)	13	1.44 (0.73-2.83)
6 repeat/8 repeat	136	87	0.81 (0.59-1.10)	20	0.85 (0.49-1.47)	16	0.68 (0.38-1.23)	66	0.94 (0.66-1.34)	16	0.65 (0.36-1.18)	23	0.88 (0.53-1.49)
8 repeat/8 repeat	11	6	0.69 (0.25-1.90)	0		1	0.53 (0.07-4.17)	7	1.24 (0.46-3.34)	4	2.04 (0.61-6.78)	2	1.00 (0.21-4.71)
Others	25	20	1.01 (0.55-1.87)	1	0.24 (0.03-1.78)	2	0.46 (0.11-2.01)	10	0.72 (0.33-1.55)	3	0.63 (0.18-2.19)	4	0.77 (0.26-2.31)
4-repeat allele													
No	494	367	1.00 (reference)	75	1.00 (reference)	74	1.00 (reference)	261	1.00 (reference)	85	1.00 (reference)	96	1.00 (reference)
Yes	383	247	0.87 (0.70-1.07)	50	0.87 (0.59-1.27)	42	0.73 (0.49-1.10)	204	1.03 (0.82-1.30)	68	1.05 (0.74-1.49)	87	1.18 (0.86-1.63)
One copy	315	216	0.92 (0.74-1.15)	41	0.86 (0.57-1.29)	38	0.80 (0.53-1.22)	179	1.11 (0.87-1.41)	63	1.18 (0.83-1.70)	74	1.24 (0.88-1.74)
Two copies	68	31	0.61 (0.39-0.96)	9	0.90 (0.43-1.89)	4	0.39 (0.14-1.11)	25	0.69 (0.42-1.12)	5	0.43 (0.17-1.10)	13	0.97 (0.51-1.83)
6-repeat allele													
No	137	76	1.00 (reference)	13	1.00 (reference)	13	1.00 (reference)	71	1.00 (reference)	25	1.00 (reference)	31	1.00 (reference)
Yes	742	538	1.31 (0.97-1.77)	112	1.59 (0.87-2.91)	103	1.47 (0.80-2.69)	394	1.02 (0.74-1.40)	128	0.91 (0.57-1.46)	152	0.89 (0.58-1.37)
One copy	410	278	1.22 (0.89-1.68)	57	1.45 (0.77-2.74)	47	1.21 (0.63-2.30)	212	1.01 (0.72-1.42)	64	0.83 (0.50-1.39)	84	0.91 (0.57-1.44)
Two copies	330	260	1.42 (1.03-1.97)	55	1.77 (0.93-3.34)	56	1.81 (0.96-3.42)	182	1.03 (0.72-1.45)	64	1.00 (0.60-1.66)	68	0.87 (0.54-1.40)
8-repeat allele													
No	680	488	1.00 (reference)	102	1.00 (reference)	92	1.00 (reference)	357	1.00 (reference)	119	1.00 (reference)	143	1.00 (reference)
Yes	199	126	0.89 (0.69-1.14)	23	0.75 (0.46-1.21)	24	0.88 (0.55-1.42)	108	1.10 (0.83-1.44)	34	1.06 (0.70-1.61)	40	1.03 (0.70-1.52)
One copy	186	120	0.89 (0.69-1.16)	23	0.79 (0.49-1.29)	23	0.90 (0.55-1.46)	101	1.09 (0.82-1.44)	30	0.99 (0.64-1.53)	38	1.03 (0.69-1.53)
Two copies	11	6	0.76 (0.28-2.07)	0		1	0.66 (0.08-5.21)	7	1.28 (0.48-3.41)	4	2.23 (0.68-7.31)	2	0.97 (0.21-4.49)

Table 3. Age-adjusted OR (95% CI) for *CYP17A1* and *HSD17B1* genotypes and risk of breast cancer and fibrocystic breast conditions, overall and by proliferation status of nontumor breast tissue

Genotype	Controls	Breast cancer						Fibrocystic breast conditions					
		Overall		Nonproliferative		Proliferative		Overall		Nonproliferative		Proliferative	
	n	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
CYP17A1 rs743572													
A1A1	138	102	1.00 (reference)	26	1.00 (reference)	16	1.00 (reference)	78	1.00 (reference)	25	1.00 (reference)	26	1.00 (reference)
A1A2 or A2A2	739	513	0.94 (0.71-1.24)	99	0.69 (0.43-1.10)	100	1.16 (0.66-2.02)	389	0.98 (0.72-1.34)	129	1.00 (0.63-1.61)	158	1.19 (0.75-1.87)
A1A2	441	297	0.91 (0.67-1.22)	55	0.64 (0.38-1.06)	62	1.20 (0.67-2.15)	233	0.99 (0.71-1.38)	81	1.06 (0.65-1.74)	87	1.11 (0.68-1.79)
A2A2	298	216	0.98 (0.72-1.33)	44	0.77 (0.45-1.30)	38	1.09 (0.59-2.03)	156	0.97 (0.69-1.37)	48	0.92 (0.54-1.56)	70	1.30 (0.79-2.15)
HSD17B1 rs605059													
GG	305	209	1.00 (reference)	44	1.00 (reference)	40	1.00 (reference)	149	1.00 (reference)	46	1.00 (reference)	58	1.00 (reference)
GA or AA	569	405	1.03 (0.83-1.28)	81	0.97 (0.65-1.43)	76	1.01 (0.67-1.52)	316	1.18 (0.93-1.51)	107	1.29 (0.88-1.88)	125	1.19 (0.84-1.68)
GA	417	289	1.01 (0.80-1.27)	64	1.05 (0.70-1.59)	53	0.97 (0.62-1.50)	236	1.21 (0.93-1.56)	81	1.33 (0.90-1.98)	92	1.19 (0.83-1.71)
AA	152	116	1.11 (0.82-1.49)	17	0.74 (0.41-1.34)	23	1.15 (0.66-1.98)	80	1.13 (0.80-1.58)	26	1.17 (0.69-1.98)	33	1.19 (0.74-1.91)

meaningful differences in the observed associations was low (Supplementary Table S1).

Discussion

Our study adds to the growing body of knowledge on genetic susceptibility to female breast cancer by examining whether common variants in the *CYP11A1*, *CYP17A1*, and *HSD17B1* genes influence the development of benign and malignant breast lesions among Chinese women. We observed an association of the *CYP11A1* pentanucleotide repeat polymorphism with risk of breast cancer but not fibrocystic breast conditions. Relative to women homozygous for the 6-repeat allele, women homozygous for the 4-repeat allele had a 42% decreased risk of breast cancer. By contrast, we found no associations between the *CYP17A1* rs743572 and *HSD17B1* rs605059 single nucleotide polymorphisms and risk of breast cancer or fibrocystic breast conditions.

Our results are best compared with those from the initial study to examine the relationship between the *CYP11A1* pentanucleotide repeat [$(TAAAA)_n$] polymorphism and breast cancer risk, also conducted in Shanghai, China (4). Most common in both study populations were the 4, 6, and 8 repeat alleles. Zheng et al. (4) found case-control differences in the frequency of the 6-repeat (cases, 62.9%; controls, 65.9%) and 8-repeat (cases, 12.6%; controls, 8.5%) alleles but not in the frequency of the 4-repeat allele (cases, 23.5%; controls, 24.2%). In their study, heterozygous and homozygous carriers of the 8-repeat allele, relative to noncarriers, had a 1.5- and 2.9-fold excess risk of breast cancer, respectively. In comparison, we noted differences in the frequency of the 4-repeat (cases, 22.6%; controls, 25.7%) and 6-repeat (cases, 65.0%; controls, 61.0%) alleles but not in the frequency of the 8-repeat allele (cases, 10.7%; controls, 11.9%). We thus failed to confirm the reported association of the 8-repeat allele and instead observed an inverse association between homozygous carriage of the 4-repeat allele and breast cancer risk. The latter association was observed irrespective of whether homozygous carriers of the 6-repeat allele or noncarriers of the 4-repeat allele served as the reference group. When we calculated risk estimates of breast cancer associated with carriage of the 4-repeat allele from Zheng et al.'s published data, the crude ORs (95% CIs) calculated for one or two (versus no) copies of the 4-repeat allele were 1.03 (0.85-1.23) and 0.82 (0.57-1.19), respectively. The corresponding age-adjusted estimates from our study were 0.92 (0.74-1.15) and 0.61 (0.39-0.96), respectively.

The only other study in which this *CYP11A1* polymorphism has been examined in relation to breast cancer is the Multiethnic Cohort (6). The results from the Multiethnic Cohort cannot be compared directly with ours or of Zheng et al.'s (4), because the analyses done are based on haplotype rather than genotype and the cohort does not include Chinese women. In this study, an elevated risk of breast cancer was associated with one of several haplotypes carrying the 6-repeat allele, but not with any of the haplotypes carrying the 8-repeat allele, when compared with the most common haplotype carrying the 4-repeat allele exclusively, suggesting, as do our results, that the 8-repeat allele does not affect breast cancer susceptibility. However, differences in *CYP11A1* expression were recently reported by Yaspan et al. (5), who compared Chinese lymphoblastoid transformed cell lines, specifically two lines homozygous for a haplotype, including the 8-repeat allele, against two lines homozygous for each of two most common haplotypes, including the 6-repeat allele, and found much higher expression in those lines carrying the haplotype with the 8-repeat allele.

With studies of haplotype-based variation in *CYP11A1* and breast cancer reporting potential risk-bearing haplotypes (5, 6), and given that the cytochrome *P*450scc enzyme encoded by the *CYP11A1* gene catalyzes the first rate-limiting step in sex steroid hormone biosynthesis from cholesterol, it is plausible that one or more

CYP11A1 variants affect a woman's risk of breast cancer. The *CYP11A1* promoter is composed of multiple *cis*-acting response elements that control transcriptional activity by binding with *trans*-acting factors (37). Thus, polymorphisms located within or near these regulatory regions, such as D15S520, may especially influence *CYP11A1* expression or cytochrome *P*450scc enzyme activity, although which, if any, do so are unknown.

With respect to the D15S520 polymorphism, correlations between the number of TAAAA repeats and levels of estrogens and androgens in women have not been demonstrated. Among postmenopausal controls in the aforementioned study in Shanghai, blood sex hormone levels were fairly similar between carriers and noncarriers of the 8-repeat allele (4). Likewise, differences in sex hormone levels according to D15S520 genotype in healthy Caucasian women have not been detected (7, 38-40), although due to sample size constraints most analyses have only compared levels between women with at least one copy of the 4-repeat allele and women without this allele. Given the lack of direct evidence that allelic variation at the D15S520 locus affects sex steroid hormone levels, the associations observed could be alternatively explained by other variants in linkage disequilibrium either within or outside of the *CYP11A1* gene.

Our findings are fairly compatible with those of prior studies examining the *CYP17A1* rs743572 and *HSD17B1* rs605059 polymorphisms in relation to breast cancer risk among Chinese women. None have reported evidence of an overall association between the *CYP17A1* variant and breast cancer risk (15, 41-43). In contrast to our study, the study by Wu et al. (15) that examined both of these variants found an elevated risk of breast cancer associated with the *HSD17B1* AA (versus GG or GA) genotype, specifically among postmenopausal women (OR, 1.86; 95% CI, 1.14-3.03). In addition, the combined effect of parity and age at first birth (that is, age at first birth >30 years or nulliparity versus age at first birth ≤30 years) on breast cancer risk was most pronounced among postmenopausal women carrying the *HSD17B1* AA genotype or the *CYP17A1* A2 allele. It should be noted, however, that the total number of subjects included in their study (188 cases and 671 controls) was much smaller than in ours, and with only 30% of their subjects classified as premenopausal, their observed difference in risk by menopausal status may have arisen by chance.

Assessing the risk of fibrocystic breast conditions associated with each selected polymorphism allowed us to investigate whether any of the three polymorphisms influence susceptibility to breast cancer through the promotion of cell proliferation. In the present study, we found no relationship between the genotype of any of the polymorphisms considered and risk of fibrocystic breast conditions or specifically of such conditions with histologic evidence of cell proliferation. This suggests that variation at these loci is not likely influential in producing cell proliferation in the mammary epithelium. Yet as this is the first study to examine polymorphisms in steroid hormone biosynthesis genes and fibrocystic breast conditions, other studies should be conducted to confirm our results.

Limitations of the present study include its size and evaluation of a single polymorphism in each gene. Although this study was larger than the previous studies examining the *CYP17A1* and *HSD17B1* single nucleotide polymorphisms in Chinese women, we may have still failed to detect small alterations in risk of breast cancer or fibrocystic breast conditions that are truly associated with these variants. Limited statistical power also likely hindered our ability to detect potential differences in risk between the subgroups of women defined by proliferation status, menopausal status, and BMI. In particular, with histologic classification of benign mammary gland tissue restricted to cases diagnosed after September 1995 who had adequate tissue for classification, proliferation status of the extratumoral tissue was determined for only 39% of all breast cancer cases. Any misclassification of proliferation status would most likely be nondifferential with respect to genotype of any polymorphism and thus could have obscured true stratum-specific differences in risk. In this context, our finding of a marked inverse relationship between homozygous carriage of the 4-repeat allele and breast cancer risk among women with concurrent extratumoral proliferation, although possibly due to chance, cannot be explained by such bias and warrants confirmation in other studies. Lastly, the null associations observed do not exclude the possibility that other variants in these genes influence susceptibility for developing fibrocystic breast conditions or breast cancer.

In conclusion, our data suggest that homozygous carriage of the *CYP11A1* 4-repeat allele is inversely related to breast cancer risk in Chinese women. To establish an etiologic connection, however, additional studies are needed to replicate our findings and to determine whether common allelic variation at this *CYP11A1* locus affects *CYP11A1* expression or cytochrome *P*450scc enzyme activity levels.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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