Polymorphisms and Haplotypes in the *Caspase-3*, *Caspase-7*, and *Caspase-8* Genes and Risk for Endometrial Cancer: A Population-Based, Case-Control Study in a Chinese Population

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Abstract

Caspase-3, caspase-7, and caspase-8 are important caspases in the apoptosis pathway and play an important role in the development and progression of cancer. We examined the association between genetic variants in the *caspase-3*, *caspase-7*, and *caspase-8* genes and risk for endometrial cancer among Chinese women. Genotypes for 1,028 women with endometrial cancer and 1,003 healthy controls were determined with the Affymetrix MegAllele Targeted Genotyping System and Molecular Inversion Probe method. Of 35 selected single-nucleotide polymorphisms, four in the *caspase-7* gene were in high linkage disequilibrium (rs11593766, rs3124740, rs11196445, and rs11196418) and associated with the risk for endometrial cancer. The *AA* genotype of rs11196418 [odds ratio, 0.36; 95% confidence interval (95% CI), 0.14-0.94] and the *G* allele of rs11593766 were associated with reduced risk (odds ratio of 0.75 and 95% CI of 0.59-0.96 for carriers of one *G* allele; odds ratio of 0.70 and 95% CI of 0.24-2.03 for carriers of two *G* alleles). The *AA* genotype of rs11196445 (odds ratio, 1.74; 95% CI, 0.99-3.05), the *CC* genotype of rs3124740 (odds ratio, 1.36; 95% CI, 1.06-1.75), and the *GG* genotype of rs10787498 in the *caspase-7* gene (odds ratio, 1.90; 95% CI, 1.16-3.11) were associated with increased risk compared with homozygotes of the major alleles. The gene-disease association seemed to be more pronounced among premenopausal women, although tests for multiplicative interaction between genes and menopausal status failed to reach statistical significance. The *GG* genotype of rs2705901 in the *caspase-3* gene was significantly associated with increased cancer risk compared with the *CC* genotype (odds ratio, 2.25; 95% CI, 1.03-4.95). No association was observed between polymorphisms of the *caspase-8* gene and risk for endometrial cancer. These findings suggest that genetic variants in caspase-3 and caspase-7 may play a role in endometrial cancer susceptibility. (Cancer Epidemiol Biomarkers Prev 2009;18(7):2114–22)

Introduction

Endometrial cancer is the second most common gynecologic cancer in the world (1). Early age at menarche, late age at menopause, nulliparity, obesity, use of hormone replacement therapy, and use of tamoxifen are well-established risk factors for endometrial cancer. Recently, it has been increasingly recognized that genetic polymorphisms may play an important role in the development of endometrial cancer. The most studied are the steroid metabolism pathway genes (2-4), cell-cycle control pathway genes (5-7), and DNA repair pathway genes (8, 9).

Apoptosis is a selective process for deleting cells in various biological systems and plays an essential role in the development and maintenance of tissue homeostasis in multicellular organisms (10). During apoptosis in humans, initiator caspases integrate molecular signals into proteolytic activity (11) and subsequently activate the downstream effector caspases, thus transmitting and amplifying the apoptotic signal (12). Inappropriate regulation of apoptosis is believed to be the cause of many human diseases, including cancer (13). *Caspase-3* and *caspase-7* have been identified as key executors of apoptosis in mammalian cells and play a central role in the execution phase of apoptosis (14, 15). *Caspase-8* is a cysteine protease, which cleaves downstream substrates such as effector caspases, to initiate the apoptotic cascade and transmit apoptotic signals downstream of death receptors (16). The expression levels of caspases in tumors are found to be distinct from levels in normal tissue in a series of cancers. For example, expression of caspase-3 was observed to be down-regulated in pediatric neuroblastoma (17), breast cancer (18), and gastric carcinoma (19), whereas caspase-7 was found to be down-regulated in colonic carcinoma (20), breast cancer (21), and gastric cancer (22). Decreased expression of

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caspase-8 was also reported in neuroblastoma (23) and pediatric tumors (24).

Genetic polymorphisms in the caspase genes may affect cancer risk through altering expression levels and functions of these genes. Several polymorphisms have been linked to susceptibility to a growing list of cancers in recent years. Yang et al. (25) found that a six-nucleotide deletion polymorphism in the *caspase-8* gene (-652 6N ins->del) decreased the risk for pancreatic cancer. Hosgood et al. (26) studied associations between polymorphisms in *caspase-3*, *caspase-8*, *caspase-9*, and *caspase-10*, and susceptibility to multiple myeloma, and found that the *TT* genotype of the *caspase-3* rs1049216 single-nucleotide polymorphism was associated with a 5-fold decrease in risk, and the *AG* and *AA* genotypes of the *caspase-9* rs1052576 single-nucleotide polymorphism were associated with decreased cancer risk. Other malignancies evaluated include cancers of lung (27), colon and rectum (28), stomach (29), breast (30), and ovary (31). Little is known about associations with endometrial cancer.

In this study, we analyzed a set of functional and tagging single-nucleotide polymorphisms in the *caspase-3*, *caspase-7*, and *caspase-8* genes in association with endometrial cancer.

Materials and Methods

Study Participants. Details of the study methods have been described elsewhere (32, 33). Briefly, 1,449 women newly diagnosed with endometrial cancer, who were 30 to 69 years of age, were identified between 1997 and 2003 through the population-based Shanghai Cancer Registry; 1,199 cases (82.7%) participated in the study. Controls were randomly selected from the general population of urban Shanghai and were identified by using the Shanghai Resident Registry, according to the age distribution of endometrial cancer cases in 1996. Women with a history of any cancer or hysterectomy were not eligible. Of the 1,629 eligible women contacted, 1,212 (74.4%) participated in the study. Study protocols were approved by the institutional review boards of all institutes involved in the study, and all participants provided written, informed consent before participating in the study.

Study participants were interviewed in person by trained retired medical professionals using a structured questionnaire. Detailed information on demographic factors, menstrual and reproductive history, hormone use, disease history, physical activity, tobacco and alcohol use, diet, weight history, and family history of cancer were collected for all participants. Body weight, height, and circumferences of the waist and hips were measured according to a standardized protocol at the time of interview. Menopause was defined as the cessation of the menstrual period for at least 12 mo before the reference date (diagnosis date for the cases and interview date for the controls), excluding lapses caused by pregnancy, breastfeeding, or estrogen hormone use. Body mass index (weight in kilograms per height in square meters) and waist-to-hip circumference ratio were calculated using measured anthropometrics.

Of the study participants who completed an in-person interview, 850 cases and 853 controls donated a blood sample and 280 cases and 274 controls provided a buccal cell sample. One hundred eighty-seven cases and 186 controls provided samples using a mouthwash method, and 93 cases and 88 controls provided samples using a buccal swab method. Because of the very low DNA yield of the buccal swab method, we did not include buccal swab DNA samples in the genotyping. In addition, DNA samples from 19 controls who donated a blood sample were used up in other studies. Thus, DNA samples from 1,037 cases (86.5%; 850 blood and 187 buccal cell) and 1,020 controls (84.2%; 834 blood and 186 buccal cell) were included in the genotyping study. Genotyping data for the caspase genes were obtained from 1,028 cases and 1,003 controls, a success rate of 99.1% and 99.6%, respectively.

Single-Nucleotide Polymorphism Selection, Identification, and Genotyping. Known nonsynonymous single-nucleotide polymorphisms and tagging single-nucleotide polymorphisms were selected for the study. Tagging single-nucleotide polymorphisms were selected by searching Han Chinese data from the HapMap

Table 1. Comparison of cases and controls with genotyping data on demographic characteristics and selected risk factors for endometrial cancer, the Shanghai Endometrial Cancer Study, 1997 to 2003

Participant characteristics	Cases (n = 1,028)	Controls (n = 1,003)	P*
Age (y; $\bar{x}$ ± SD)	54.3 ± 8.5	54.4 ± 8.5	0.87
≥Middle school education (%)	78.3	78.0	0.85
Regular smoker (%)	3.1	3.6	0.55
Regular alcohol consumption (%)	3.1	5.3	0.01
First degree relative with cancer (%)	35.7	29.6	<0.01
Age at menarche ($\bar{x}$ ± SD)	14.5 ± 1.7	14.8 ± 1.8	<0.01
Postmenopausal (%)	56.8	61.5	0.03
Age at menopause† ($\bar{x}$ ± SD)	50.3 ± 3.6	49.0 ± 3.6	<0.01
Years of menstruation ($\bar{x}$ ± SD)	32.8 ± 4.9	30.7 ± 5.3	<0.01
Number of live births ($\bar{x}$ ± SD)	2.6 ± 1.4	2.8 ± 1.3	<0.01
Ever used oral contraceptives (%)	18.0	25.3	<0.01
Ever used hormone replacement therapy (%)	4.8	4.4	0.68
Diagnosis of diabetes (%)	15.1	6.9	<0.01
Body mass index ($\bar{x}$ ± SD)	25.8 ± 4.1	23.8 ± 3.5	<0.01
Waist-to-hip ratio ($\bar{x}$ ± SD)	0.84 ± 0.05	0.82 ± 0.06	<0.01
Engaged in regular physical activity (%)	28.2	33.9	<0.01

*For χ^2 test (categorical variables) or nonparameter Wilcoxon test (continuous variables).
†Only among postmenopausal women.

Table 2. Association of genetic variants in *caspase-3*, *caspase-7*, and *caspase-8* genes with endometrial cancer risk, the Shanghai Endometrial Cancer Study, 1997 to 2003

Gene	SNP	Alleles	Gene region	Case/controls (1,028/1,003)			
				OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡	P§
CASP3	rs4647693	G/A	Intron	1.01 (0.83-1.22)	1.04 (0.64-1.69)	1.01 (0.86-1.19)	0.88
	rs2705901	C/G	Boundary	0.91 (0.73-1.12)	2.25 (1.03-4.95)	1.02 (0.84-1.23)	0.86
	rs2720378	G/C	Intron	1.10 (0.92-1.33)	0.92 (0.68-1.25)	1.01 (0.89-1.16)	0.86
	rs2705881	A/G	Promoter	1.06 (0.89-1.28)	0.85 (0.61-1.18)	0.98 (0.86-1.12)	0.77
CASP7	rs12415607	C/A	Promoter	0.88 (0.73-1.07)	0.98 (0.75-1.28)	0.97 (0.85-1.10)	0.59
	rs11196418	G/A	Promoter	1.04 (0.83-1.30)	0.36 (0.14-0.94)	0.94 (0.76-1.14)	0.51
	rs7922608	T/G	Intron	0.99 (0.82-1.18)	1.33 (0.92-1.93)	1.07 (0.93-1.23)	0.37
	rs11593766	T/G	Non-synonymous	0.75 (0.59-0.96)	0.70 (0.24-2.03)	0.76 (0.61-0.96)	0.02
	rs11196438	A/G	Intron	1.02 (0.81-1.27)	0.39 (0.15-1.01)	0.93 (0.76-1.13)	0.46
	rs11196444	G/C	Intron	0.99 (0.78-1.26)	2.45 (0.77-7.84)	1.06 (0.85-1.33)	0.59
	rs3124740	G/C	Intron	1.03 (0.85-1.26)	1.36 (1.06-1.75)	1.15 (1.01-1.30)	0.03
	rs11196445	G/A	Intron	1.11 (0.91-1.35)	1.74 (0.99-3.05)	1.17 (0.99-1.39)	0.06
	rs3127075	G/C	Intron	1.01 (0.83-1.22)	1.20 (0.72-1.99)	1.04 (0.88-1.22)	0.68
	rs17090904	C/T	Intron	0.82 (0.67-1.01)	0.97 (0.76-1.23)	0.98 (0.86-1.10)	0.68
	rs12359418	C/T	Intron	1.01 (0.80-1.26)	0.39 (0.12-1.25)	0.94 (0.76-1.16)	0.57
	rs12416109	A/G	Intron	1.06 (0.87-1.29)	1.14 (0.90-1.44)	1.07 (0.95-1.20)	0.27
	rs6585241	A/G	Intron	1.09 (0.90-1.32)	1.33 (0.81-2.20)	1.11 (0.95-1.30)	0.20
	rs10787498	T/G	3UTR	0.91 (0.75-1.10)	1.90 (1.16-3.11)	1.06 (0.91-1.24)	0.47
	rs12247479	G/A	3UTR	0.97 (0.78-1.21)	2.23 (0.91-5.46)	1.06 (0.87-1.29)	0.59
	rs1127687	G/A	3UTR	1.00 (0.83-1.21)	0.77 (0.53-1.13)	0.94 (0.81-1.09)	0.40
	rs17090919	G/A	3UTR	1.10 (0.90-1.34)	1.04 (0.58-1.87)	1.07 (0.90-1.28)	0.42
	rs10885497	C/G	3UTR	1.14 (0.86-1.52)	1.98 (0.36-10.81)	1.17 (0.89-1.53)	0.27
CASP8	rs6747918	G/A	Promoter	1.03 (0.85-1.24)	1.16 (0.80-1.69)	1.05 (0.91-1.22)	0.49
	rs12620010	T/G	Intron	1.02 (0.84-1.23)	1.29 (0.88-1.88)	1.07 (0.93-1.24)	0.34
	rs3769827	T/C	3UTR	1.02 (0.85-1.23)	1.21 (0.83-1.75)	1.06 (0.92-1.22)	0.43
	rs3769826	T/G	3UTR	0.98 (0.82-1.19)	1.14 (0.80-1.64)	1.03 (0.89-1.18)	0.71
	rs7608692	G/A	5UTR	1.07 (0.89-1.29)	0.99 (0.73-1.35)	1.02 (0.70-1.17)	0.73
	rs3769825	T/C	5UTR	1.01 (0.83-1.22)	1.15 (0.77-1.71)	1.04 (0.89-1.20)	0.63
	rs3754935	T/G	5UTR	1.07 (0.89-1.29)	1.30 (0.90-1.86)	1.10 (0.96-1.27)	0.17
	rs10931934	C/T	5UTR	1.09 (0.87-1.36)	1.11 (0.87-1.42)	1.05 (0.93-1.19)	0.42
	rs3769823	C/T	5UTR	1.03 (0.86-1.24)	0.81 (0.58-1.14)	0.96 (0.84-1.10)	0.55
	rs1861270	C/T	Intron	1.02 (0.85-1.22)	0.77 (0.55-1.08)	0.94 (0.82-1.08)	0.38
	rs3754934	G/T	3UTR	1.02 (0.85-1.23)	1.22 (0.83-1.79)	1.06 (0.92-1.22)	0.44
	rs1045487	G/A	Synonymous	1.02 (0.85-1.23)	0.99 (0.67-1.48)	1.01 (0.87-1.17)	0.90
	rs700636	A/C	Flanking	0.99 (0.80-1.22)	1.01 (0.79-1.29)	1.00 (0.89-1.14)	0.96

Abbreviations: AA, major allele homozygotes; BB, minor allele homozygotes, AB, heterozygotes; FR, flanking region; CASP, caspase; SNP, single-nucleotide polymorphism; OR, odds ratio.
*AA reference group; estimates for AB genotype, adjusted for age.
†AA reference group; estimates for BB genotype, adjusted for age.
‡Age-adjusted odds ratio for per allele.
§*P* value for trend test from additive models of effect.

project[4] using the Tagger program (34), and nonsynonymous single-nucleotide polymorphisms were identified by review of literature and existing databases. The following criteria were used to identify tagging single-nucleotide polymorphisms: (*a*) single-nucleotide polymorphisms located in the genes or within the 5-kb region flanking the genes, (*b*) a minor allele frequency ≥0.05, and (*c*) other unselected single-nucleotide polymorphisms could be captured by one of the tagging single-nucleotide polymorphisms with a linkage disequilibrium of $r^2 \geq 0.90$. Single-nucleotide polymorphism selection was completed in December of 2005. As a result, a total of 34 tagging single-nucleotide polymorphisms and one nonsynonymous single-nucleotide polymorphism were identified.

The single-nucleotide polymorphisms were genotyped using the Affymetrix MegAllele Targeted Genotyping System with the Molecular Inversion Probe method (35) as part of a large-scale genotyping effort that included 1,737 single-nucleotide polymorphisms. Genotyping was conducted at the Vanderbilt Microarray Shared Resource, following the manufacturer's protocol. Briefly, 2.01 μg of genomic DNA was annealed to the assay panel overnight at 58°C. After annealing, the samples were split into four equal aliquots. Each aliquot was gap filled with four different aliquots receiving a different deoxynucleotide triphosphate. The deoxynucleotide triphosphate was ligated to produce a padlocked probe and then digested with exonucleases. The padlocked probe was then cleaved at a specific cleavage site and inverted. The inverted probe was the substrate for two rounds of PCR. After passing quality control (QC) tests, samples were hybridized to the arrays. Arrays were then washed, stained, detected via the scanner, and analyzed by using the Affymetrix protocol.

As a QC procedure, we included 39 blinded duplicate samples and 12 HapMap DNA samples in the genotyping. The average consistency rate for these samples was 99.6%; the lowest consistency rate was 97.4%. The

[4] www.hapmap.org

Table 3. Association of genetic variants in *caspase-7* gene with endometrial cancer risk by menopausal status, the Shanghai Endometrial Cancer Study, 1997 to 2003

Genotypes	Cases (%)	Controls (%)	*P*	Age-adjusted OR (95% CI)	OR per allele	*P* for trend
Premenopausal women						
rs11196418						
GG	362 (81.5)	300 (77.9)	0.10	1.00		
AG	80 (18.0)	78 (20.3)		0.86 (0.61-1.22)		
AA	2 (0.5)	7 (1.8)		0.24 (0.05-1.17)	0.78 (0.57-1.07)	0.12
GA/AA	82 (18.5)	85 (22.1)	0.20	0.81 (0.58-1.14)		
rs11593766						
TT	387 (87.4)	308 (80.0)	0.02	1.00		
GT	54 (12.2)	75 (19.5)		0.56 (0.38-0.82)		
GG	2 (0.5)	2 (0.5)		0.94 (0.13-6.74)	0.60 (0.42-0.86)	<0.01
GT/GG	56 (12.6)	77 (20.0)	<0.01	0.57 (0.39-0.83)		
rs3124740						
GG	151 (34.0)	137 (35.5)	0.08	1.00		
CG	206 (46.4)	196 (50.8)		0.96 (0.71-1.30)		
CC	87 (19.6)	53 (13.7)		1.51 (1.00-2.29)	1.17 (0.96-1.43)	0.12
CG/CC	293 (66.0)	249 (64.5)	0.65	1.08 (0.81-1.44)		
rs11196445						
GG	295 (67.2)	286 (74.5)	0.02	1.00		
AG	126 (28.7)	92 (24.0)		1.29 (0.94-1.77)		
AA	18 (4.1)	6 (1.6)		2.95 (1.15-7.56)	1.41 (1.08-1.85)	0.01
AG/AA	144 (32.8)	98 (25.5)	0.02	1.39 (1.03-1.89)		
rs10787498						
TT	280 (63.1)	255 (66.2)	0.23	1.00		
GT	143 (32.2)	120 (31.2)		1.09 (0.81-1.47)		
GG	21 (4.7)	10 (2.6)		1.94 (0.89-4.22)	1.19 (0.93-1.53)	0.17
TG/GG	164 (36.9)	130 (33.8)	0.34	1.15 (0.87-1.54)		
Postmenopausal women						
rs11196418						
GG	463 (79.3)	501 (81.3)	0.21	1.00		
GA	117 (20.0)	106 (17.2)		1.20 (0.90-1.61)		
AA	4 (0.7)	9 (1.5)		0.48 (0.15-1.57)	1.08 (0.83-1.40)	0.59
GA/AA	121 (20.7)	115 (18.7)	0.37	1.14 (0.86-1.52)		
rs11593766						
TT	496 (85.2)	516 (83.8)	0.72	1.00		
GT	82 (14.1)	94 (15.3)		0.91 (0.66-1.26)		
GG	4 (0.7)	6 (1.0)		0.69 (0.19-2.46)	0.89 (0.67-1.20)	0.45
GT/GG	86 (14.8)	100 (16.2)	0.49	0.90 (0.66-1.23)		
rs3124740						
GG	175 (30.0)	205 (33.3)	0.23	1.00		
CG	280 (48.0)	298 (48.4)		1.10 (0.85-1.43)		
CC	128 (22.0)	113 (18.3)		1.33 (0.96-1.83)	1.15 (0.98-1.35)	0.09
CG/CC	408 (70.0)	411 (66.7)	0.23	1.16 (0.91-1.49)		
rs11196445						
GG	407 (70.3)	432 (70.4)	0.86	1.00		
AG	156 (26.9)	168 (27.4)		0.99 (0.76-1.28)		
AA	16 (2.8)	14 (2.3)		1.21 (0.58-2.52)	1.02 (0.82-1.27)	0.85
AG/AA	172 (29.7)	182 (29.6)	0.98	1.00 (0.78-1.29)		
rs10787498						
TT	395 (67.6)	398 (64.5)	0.02	1.00		
TG	161 (27.6)	204 (33.1)		0.80 (0.62-1.02)		
GG	28 (4.8)	15 (2.4)		1.88 (0.99-3.58)	0.98 (0.80-1.20)	0.81
TG/GG	189 (32.4)	219 (35.5)	0.25	0.87 (0.69-1.11)		

NOTE: *P* for interaction test for menopausal status with rs11196418, rs11593766, rs3124740, rs11196445, and rs10787498 were 0.26, 0.16, 0.54, 0.16, and 0.28, respectively.

genotyping of single-nucleotide polymorphisms was highly successful, with call rates of 99.5% to 100% (median, 99.95%). Finally, the laboratory staff remained blind to the case-control status and identity of all samples.

Statistical Analyses. We used SAS software (version 9.1; SAS Institute, Inc.) for the statistical analyses. χ^2 statistics and the *t* test were used to evaluate case-control differences in the distribution of risk factors and genotypes and to determine whether allele frequencies in healthy controls deviated from Hardy-Weinberg equilibrium. Linkage disequilibrium between the polymorphisms in the *caspase-7* and *caspase-8* genes was assessed by HaploView version 4.0 (36). Haplotypes were reconstructed using HAPSTAT software (37), which uses an expectation maximization algorithm to calculate maximum likelihood estimates of haplotype frequencies while taking into account phase ambiguity (38). Logistic regression models were used to estimate odds ratios and 95% confidence intervals (95% CI) with adjustment for age. We used HAPSTAT software to evaluate associations between haplotypes and endometrial cancer risk, and interactions between haplotype and environmental exposures on endometrial cancer risk (39). We made

additional adjustments for nongenetic risk factors, including having a first-degree relative with cancer, age at menarche, age at menopause, years of menstruation, number of live births, use of oral contraceptives, body mass index, waist-to-hip ratio, and physical activity status, which did not alter the gene-disease associations (data not shown). Thus, only the age-adjusted results are reported.

Results

Our study population consisted of 1,028 endometrial cancer cases and 1,003 healthy controls. Table 1 presents a comparison of characteristics of cases and controls. Endometrial cancer cases and controls were comparable with respect to age, with a mean age of 54.3 (±8.5) years for cases and 54.4 (±8.5) years for controls. More cases (35.7%) had a family history of any cancer than did controls (29.6%; $P < 0.01$). Compared with controls, cases were more likely to be diagnosed with diabetes and have earlier age at menarche, later age at menopause, longer duration of menstruation, fewer pregnancies, and higher body mass index and waist-to-hip circumference ratio, but were less likely to regularly drink alcohol, use oral contraceptives, or regularly participate in physical activity.

The associations of endometrial cancer with single-nucleotide polymorphisms in the *caspase-3*, *caspase-7*, and *caspase-8* genes are presented in Table 2. The genotype distributions of all 35 polymorphisms under study were in Hardy-Weinberg equilibrium among controls. In the *caspase-3* gene, the *GG* genotype of rs2705901 was significantly associated with increased cancer risk compared with the *CC* genotype (odds ratio, 2.25; 95% CI, 1.03-4.95). Among the 18 single-nucleotide polymorphisms examined in the *caspase-7* gene, five variants were significantly or marginally significantly associated with endometrial cancer risk. Specifically, the *CC* genotype of rs3124740 (odds ratio, 1.36; 95% CI, 1.06-1.75; $P_{trend} = 0.03$), the *GG* genotype of rs10787498 (odds ratio, 1.90; 95% CI, 1.16-3.11), and the *AA* genotype of rs1196445 (odds ratio, 1.74; 95% CI, 0.99-3.05; $P_{trend} = 0.06$) were related to an increased risk for endometrial cancer compared with their respective common homozygous genotype. The *AA* genotype of rs11196418 (odds ratio, 0.36; 95% CI, 0.14-0.94) and the *G* allele (*GG* or *GT*) of the rs11593766 single-nucleotide polymorphism (odds ratio of 0.75 and 95% CI of 0.59-0.96 for the *GT* genotype, and odds ratio of 0.70 and 95% CI of 0.24-2.03 for the *GG* genotype; $P_{trend} = 0.02$) were associated with reduced risk for endometrial cancer. None of the 13 single-nucleotide polymorphisms under study in *caspase-8* were associated with risk for endometrial cancer.

We further evaluated the association of the rs11196418, rs11593766, rs3124740, rs11196445, and rs10787498 polymorphisms in the caspase-7 gene with endometrial cancer risk stratified by menopausal status (Table 3). The gene-disease associations seemed to be more pronounced among premenopausal women. However, no significant interaction between single-nucleotide polymorphisms and menopausal status was observed ($P > 0.05$; Table 3) nor were any significant interactions observed for rs2705901 in the *caspase-3* gene with

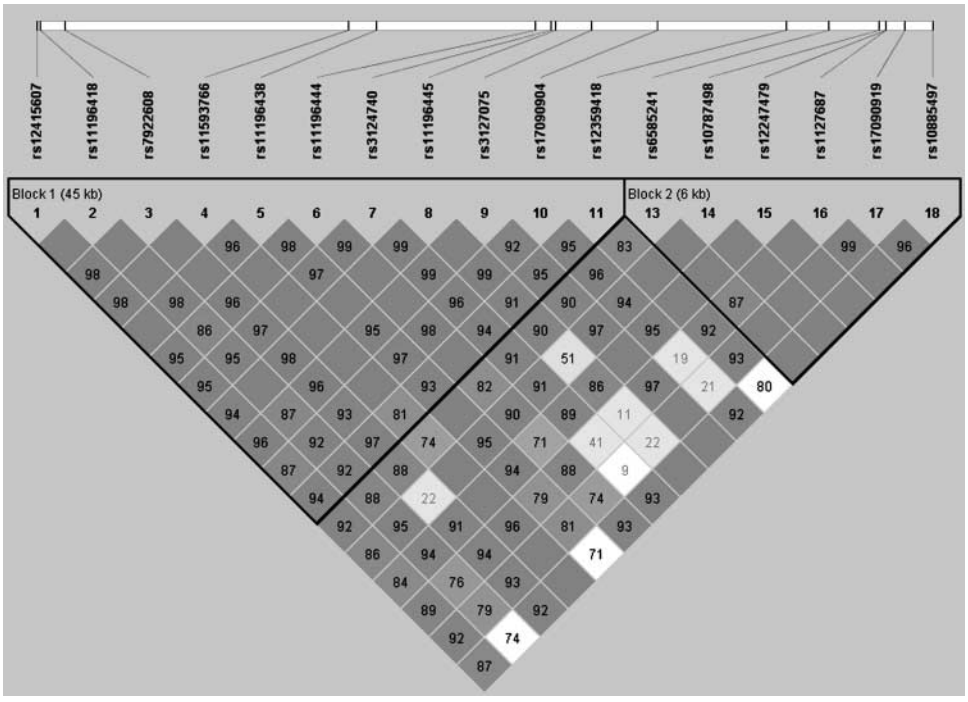

Figure 1. Pairwise linkage disequilibrium between tagging single-nucleotide polymorphisms in the *caspase-7* gene. The value within each diamond is the pairwise correlation between tagging single-nucleotide polymorphisms (measured as D'), defined by the upper left and upper right sides of the diamond. Diamonds without a number correspond to $D' = 1$. Shading, the magnitude and significance of pairwise linkage disequilibrium, with a red-to-white gradient reflecting higher-to-lower linkage disequilibrium values.

Table 4. Association of haplotypes in the *caspase-7* gene with endometrial cancer risk, the Shanghai Endometrial Cancer Study, 1997 to 2003

Haplotype	Frequency in cases (%)	Frequency in controls (%)	Age-adjusted OR (95% CI)		
			Dominant model	Additive model	Recessive model
CASP7					
Block 1*					
Hap1: AGTTAGGGGTC	35.8	35.6	1.00	1.00	1.00
Hap2: CGGTAGCGCCC	17.0	16.3	1.04 (0.86-1.26)	1.06 (0.88-1.27)	1.12 (0.76-1.65)
Hap3: CGTTAGCAGCC	16.5	14.6	1.10 (0.91-1.34)	1.13 (0.93-1.36)	1.24 (0.83-1.84)
Hap4: CATTGGGGGTT	8.7	9.0	1.01 (0.80-1.29)	0.97 (0.77-1.22)	0.35 (0.11-1.11)
Hap5: CGGTACCGGCC	8.7	8.0	1.07 (0.84-1.37)	1.11 (0.88-1.41)	1.47 (0.76-2.85)
Hap6: CGTGAGGGGCC	7.1	9.0	0.78 (0.61-1.00)	0.80 (0.63-1.02)	0.90 (0.39-2.07)
Block 2†					
Hap1: ATGGGC	39.4	40.7	1.00	1.00	1.00
Hap2: GTGGGC	18.0	16.5	1.08 (0.89-1.31)	1.13 (0.94-1.35)	1.21 (0.84-1.75)
Hap3: AGAGGC	11.0	10.5	1.02 (0.82-1.28)	1.09 (0.88-1.35)	1.44 (0.85-2.45)
Hap4: ATGAAC	15.2	14.2	1.08 (0.89-1.32)	1.11 (0.92-1.33)	1.06 (0.69-1.65)
Hap5: AGGGGG	5.8	5.1	1.15 (0.86-1.53)	1.19 (0.90-1.58)	1.35 (0.49-3.74)
Hap6: ATGAGC	7.2	9.3	0.77 (0.60-0.98)	0.79 (0.62-1.00)	0.71 (0.29-1.75)
Hap7: AGGGGC	2.7	3.1	0.92 (0.63-1.34)	0.92 (0.63-1.33)	—

*In the order rs12415607, rs11196418, rs7922608, rs11593766, rs11196438, rs11196444, rs3124740, rs11196445, rs3127075, rs17090904, and rs12359418.
†In the order rs6585241, rs10787498, rs12247479, rs1127687, rs17090919, and rs10885497.

menopausal status ($P_{interaction}$ = 0.72; data not shown in table). We further evaluated the interactive effect of other risk factors such as smoking, alcohol consumption, age at menarche, and years of menstruation on the rs11196418, rs11593766, rs3124740, rs11196445, and rs10787498 polymorphisms, and no significant interaction was observed.

The genetic variants under study in *caspase-7* fall into two major haplotype blocks, as shown in Fig. 1. rs11196418, rs3124740, rs11593766, and rs11196445 were located in the same haplotype block and were in close linkage disequilibrium ($r^2 \geq 0.95$).

Using Hapstat software, we constructed six haplotypes in block 1 and 7 haplotypes in block 2 of the *caspase-7* gene. Table 4 lists the frequencies of the haplotypes among cases and controls. Haplotypes with frequencies below 3.0% among cases and controls were excluded from the analysis. We found that a decreased risk for endometrial cancer was associated with Hap6 in block 1, consisting of single-nucleotide polymorphisms rs12415607, rs11196418, rs7922608, rs11593766, rs11196438, rs11196444, rs3124740, rs11196445, rs3127075, rs17090904, and rs12359418 (dominant, odds ratio of 0.78 and 95% CI of 0.61-0.1.00; additive, odds ratio of 0.80 and 95% CI of 0.63-1.02 relative to Hap1), and Hap6 in block 2, consisting of single-nucleotide polymorphisms rs6585241, rs10787498, rs12247479, rs1127687, rs17090919, and rs10885497 (dominant, odds ratio of 0.77 and 95% CI of 0.60-0.98; additive, odds ratio of 0.79 and 95% CI of 0.62-1.00 relative to Hap1). Three protective alleles and one risk allele were contained in the significant Hap6 in block 1, and one protective allele was included in Hap6 in block 2.

The associations between caspase-7 haplotypes and the risk for endometrial cancer were further examined by stratifying participants according to menopausal status (Table 5). Associations of Hap6 in block 1 and Hap6 in block 2 with endometrial cancer were more pronounced in premenopausal women. However, tests for multiplicative interaction were not significant. In addition, we found that Hap2 in block 2 was associated with increased risk among postmenopausal women under dominant and additive models, and a significant multiplicative interaction between the Hap2 in block 2 and menopausal status was observed ($P_{interaction}$ = 0.0006).

Discussion

This work is the first attempt to evaluate the relationship between polymorphisms in the caspase-3, caspase-7, and *caspase-8* genes, and susceptibility to endometrial cancer. We found that one single-nucleotide polymorphism (rs2705901) in *caspase-3* and five single-nucleotide polymorphisms (rs11196418, rs11593766, rs3124740, rs11196445, and rs10787498) in *caspase-7* were associated with the risk for endometrial cancer. No significant associations were observed for variants of *caspase-8*.

Soung et al. (40) previously investigated the entire coding region and all splice sites of the *caspase-7* gene in human solid cancer tissues and normal tissues for carcinomas of the stomach, colon, head/neck, esophagus, urinary bladder, and lung, and expressed the tumor-derived *caspase-7* mutants in 293 T cells. Their data suggested that inactivating mutations of the caspase-7 gene leads to the loss of its apoptotic function and contributes to the pathogenesis of some human solid cancers. However, no epidemiologic studies have evaluated the association of *caspase-7* polymorphisms with cancer risk. In our study, we found that five single-nucleotide polymorphisms in the *caspase-7* gene, one variant in the promoter (rs11196418), one nonsynonymous mutation (rs11593766), two intron mutations (rs3124740 and rs11196445), and one variant in the 3′ untranslated region (UTR; rs10787498) were associated with the risk for endometrial cancer. Of these single-nucleotide polymorphisms, four are in close proximity and in high linkage disequilibrium. Single-nucleotide polymorphism rs11593766, which was related to decreased risk for endometrial cancer, is located in exon 2 and causes a Glu to Asp change at the N-terminal end of the protein. However, the functional significance of this change is unknown. The two polymorphisms located in

intron 2 are in very close contig positions. rs11196418 and rs10787498 are located in the promoter and 3′ UTR of the *caspase-7* gene and thus may be involved in the regulation of gene expression. Studies are needed to verify our findings and to investigate the functionality of these single-nucleotide polymorphisms and other single-nucleotide polymorphisms in the region.

Recent studies have shown the utility of haplotype analysis in studying gene-disease associations (41). In our study, Hap6 in block 1 of the *caspase-7* gene, which included three single low-risk alleles [rs11593766 (*G*), rs3124740 (*G*), and rs11196445 (*G*), and one single high-risk allele rs11196418 (*G*)], was strongly associated with decreased risk for endometrial cancer compared with Hap1 in block1, which included one more high-risk allele [rs11593766 (*T*)], confirming the findings of our single single-nucleotide polymorphism analyses. We found that Hap6 in block 2 of the caspase-7 gene, which contained one low-risk allele [rs10787498 (*T*)], was associated with decreased risk for cancer, particularly among premenopausal women. However, the only difference in alleles between Hap6 and Hap1 in block 2 was at rs1127687, which was not a variant significantly linked to endometrial cancer risk. In addition, Hap4 in block 2, which contained the same allele as Hap6, was not related to cancer risk. We observed a similar situation for the increased risk associated with Hap2 compared with Hap1 in block 2. These results suggest that polymorphisms may exert independent or interactive effects on the development of endometrial cancer.

It is believed that early age at menarche, late age at menopause, and long duration of menstruation over the course of a lifetime increase the risk for endometrial cancer because of prolonged exposure to estrogens (42). Estrogens have also been reported to affect the activity of caspases and the apoptosis of cells. For example, Thiantanawat et al. (43) found that withdrawal of estrogen from MCF-7Ca cells results in higher caspase-7 activity. Zhang et al. (44) also reported that 17-β-estradiol may prevent neuronal apoptosis and that 17-β-estradiol–treated neuronal extracts directly inhibit the recombinant activity of *caspase-3*, *caspase-6*, *caspase-7*, and *caspase-8*. Therefore, it is plausible that estrogen exposure may interact with *caspase-7* single-nucleotide polymorphisms in the etiology of endometrial cancer. Our results suggest that gene-disease associations are more pronounced among premenopausal women, although no significant interaction was observed. However, our study was not adequately powered to detect moderate interactions. Interestingly, the association of endometrial cancer risk with Hap2 in block 2 of *caspase-7* was observed to be significantly modified by menopausal

Table 5. Association of haplotypes in the *caspase-7* gene with endometrial cancer risk stratified by menopausal status, the Shanghai Endometrial Cancer Study 1997 to 2003

Haplotype	Age-adjusted OR (95% CI)		
	Dominant	Additive	Recessive
Premenopausal women			
Block 1*			
Hap1: AGTTAGGGGTC	1.00	1.00	1.00
Hap2: CGGTAGCGCCC	0.81 (0.59-1.11)	0.89 (0.66-1.21)	1.49 (0.81-2.76)
Hap3: CGTTAGCAGCC	1.20 (0.88-1.64)	1.25 (0.92-1.68)	1.52 (0.85-2.70)
Hap4: CATTGGGGGTT	0.82 (0.57-1.19)	0.78 (0.55-1.12)	0.25 (0.03-1.79)
Hap5: CGGTACCGGCC	1.12 (0.77-1.64)	1.11 (0.76-1.61)	0.91 (0.28-2.97)
Hap6: CGTGAGGGGCC	0.60 (0.40-0.88)	0.61 (0.42-0.89)	0.65 (0.15-2.71)
Block 2†			
Hap1: ATGGGC	1.00	1.00	1.00
Hap2: GTGGGC	0.78 (0.57-1.07)	0.87 (0.65-1.16)	1.29 (0.70-2.36)
Hap3: AGAGGC	1.12 (0.80-1.56)	1.16 (0.84-1.61)	1.29 (0.58-2.88)
Hap4: ATGAAC	0.96 (0.70-1.30)	1.04 (0.77-1.39)	1.41 (0.77-2.59)
Hap5: AGGGGG	1.19 (0.76-1.86)	1.25 (0.80-1.94)	1.50 (0.35-6.39)
Hap6: ATGAGC	0.59 (0.40-0.88)	0.62 (0.42-0.91)	0.67 (0.16-2.79)
Hap7: AGGGGC	0.76 (0.41-1.40)	0.76 (0.41-1.40)	—
Postmenopausal women			
Block 1*			
Hap1: AGTTAGGGGTC	1.00	1.00	1.00
Hap2: CGGTAGCGCCC	1.27 (0.99-1.63)	1.23 (0.97-1.55)	0.95 (0.57-1.58)
Hap3: CGTTAGCAGCC	1.07 (0.82-1.38)	1.08 (0.85-1.39)	1.05 (0.60-1.83)
Hap4: CATTGGGGGTT	1.20 (0.88-1.64)	1.15 (0.85-1.56)	0.43 (0.10-1.77)
Hap5: CGGTACCGGCC	1.06 (0.77-1.47)	1.15 (0.84-1.57)	1.97 (0.88-4.38)
Hap6: CGTGAGGGGCC	0.97 (0.70-1.35)	1.00 (0.73-1.38)	1.11 (0.40-3.08)
Block 2†			
Hap1: ATGGGC	1.00	1.00	1.00
Hap2: GTGGGC	1.35 (1.06-1.73)	1.34 (1.07-1.68)	1.16 (0.73-1.84)
Hap3: AGAGGC	0.95 (0.71-1.27)	1.03 (0.78-1.36)	1.52 (0.75-3.07)
Hap4: ATGAAC	1.19 (0.92-1.53)	1.16 (0.91-1.49)	0.84 (0.44-1.57)
Hap5: AGGGGG	1.13 (0.77-1.64)	1.16 (0.80-1.68)	1.23 (0.29-5.13)
Hap6: ATGAGC	0.93 (0.67-1.28)	0.94 (0.69-1.28)	0.74 (0.23-2.38)
Hap7: AGGGGC	1.06 (0.66-1.71)	1.05 (0.65-1.69)	—

NOTE: *P* for interaction tests for menopausal status with Hap6 in block 1 was 0.61 and with Hap2 and Hap6 in block 2 were 0.0006 and 0.33, respectively, under the additive model.

*In the order rs12415607, rs11196418, rs7922608, rs11593766, rs11196438, rs11196444, rs3124740, rs11196445, rs3127075, rs17090904, and rs12359418.

†In the order rs6585241, rs10787498, rs12247479, rs1127687, rs17090919, and rs10885497.

status, suggesting complex gene-gene and gene-environment interactions.

One previous study has reported that the *C* allele of *caspase-3* Ex8+567T>C (rs1049216) was associated with a decreased risk for non-Hodgkin's lymphoma (odds ratio, 0.4; 95% CI, 0.3-0.7) in a U.S. population (45). Variant alleles at the *-928A>G*, *77G>A*, and *17532A>C* positions in the *caspase-3* gene, as well as the haplotypes constructed with these polymorphisms, were linked to decreased risk for lung cancer (27). In our study, we found that a variant in *caspase-3*, rs2705901, a single-nucleotide polymorphism located in the boundary region of the *caspase-3* gene, was significantly associated with endometrial cancer risk.

Studies on associations between the *caspase-8* gene and cancer risk have generated conflicting results. Sun et al. (46) reported that the -652 6N insertion/deletion variant in *caspase-8* was associated with several kinds of tumors, including lung, esophageal, gastric, colorectal, cervical, and breast cancers in a Chinese population. A UK study (47) observed a 1.37-fold increased risk for glioma (95% CI, 1.10-1.70; $P = 0.004$) in carriers of the *caspase-8* D302H variant allele. However, neither of these variants was associated with the risk for colorectal cancer in another UK study (28). A recent multiethnic study failed to find an association between the *caspase-8* -652 6N ins/del polymorphism and cancers of the breast, colorectum, or prostate (48). The D302H polymorphism is not present in Asian populations, and in the current study, we did not find a significant association of endometrial cancer with any tagging or known non-synonymous single-nucleotide polymorphisms in the *caspase-8* gene, including rs6747918, the single-nucleotide polymorphism in close linkage disequilibrium with rs3834129 (the -652 6N ins/del variant).

Our study has several strengths. First, we used a combination of functional and tagging single-nucleotide polymorphism approaches to capture polymorphisms, which is the most comprehensive evaluation of genetic markers in the genes included in the study. Second, this study has a large sample size from a population with a relatively homogeneous ethnic background (>98% Han Chinese). Finally, the relatively high participation rate (82.8% for cases and 74.4% for controls), high DNA sample donation rate (86.5% for cases and 84.2% for controls), and low frequency of hysterectomy (5.1%) mitigate concern about selection bias. Nevertheless, chance findings cannot be excluded. Further studies are needed to replicate our findings and evaluate the mechanisms underlying the associations of caspase genes with endometrial cancer risk.

In summary, of the 35 nonsynonymous and tagging single-nucleotide polymorphisms in the *caspase-3*, *caspase-7*, and *caspase-8* genes that were investigated in this study, five variants (rs11593766, rs3124740, rs11196445, rs1196418, and rs10787498) in *caspase-7* and one (rs2705901) in *caspase-3* were associated with risk for endometrial cancer. These results warrant replication in other study populations.

Disclosure of Potential Conflicts of Interest

The authors have no conflicts of interest to disclose.

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Polymorphisms and Haplotypes in the *Caspase-3*, *Caspase-7*, and *Caspase-8* Genes and Risk for Endometrial Cancer: A Population-Based, Case-Control Study in a Chinese Population

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