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RESEARCH

Genetic Polymorphism of *CAT* C-262 T and Susceptibility to Breast Cancer, a Case–Control Study and Meta-Analysis of the Literatures

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Abstract Catalase (CAT) activity is likely to be affected by functional polymorphism of C-262 T (rs1001179) in the *CAT* gene (OMIM: 115500). It is hypothesized that individuals with the lower expressing forms of the *CAT* polymorphism may be more susceptible to breast cancer. Therefore, the present case–control study and meta-analysis were carried out. The present case–control study consisted of 407 females with breast cancer and a total of 395 healthy female from population matched with patients according to age. Genotypic analysis for the *CAT* C-262 T polymorphism was determined by PCR. We identified 7 eligible studies, including 10,471 subjects (4,959 patients, and 5,512 healthy controls) in relation to the *CAT* C-262 T polymorphism and breast cancer risk. Based on the present case–control study, the CT (OR=0.90, 95 % CI: 0.66–1.22, *P*=0.484) and TT (OR=0.68, 95 % CI: 0.35–1.30, *P*=0.245) genotypes were not associated with breast cancer risk compared to the CC genotype. For meta-analysis including all studies, there was significant heterogeneity between studies. The overall ORs of the breast cancer risk were not associated with the CT (Q-statistic=14.90, df=6, *P*<0.05; OR=1.01, 95 % CI: 0.92–1.09, *P*=0.862) and TT (Q-statistic=2.57, df=6, *P*>0.05; OR=1.03, 95 % CI: 0.85–1.24, *P*=0.770) genotypes. There was no association between C-262 T polymorphism of the *CAT* and risk of breast cancer.

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Introduction

Transient fluctuations in reactive oxygen species (ROS) have important regulatory functions, but at high and/or sustained levels, ROS can cause severe damage to DNA [1, 2]. Oxidative stress may play a significant role in the etiology of different types of cancers, including breast cancer [3–6]. The effect of ROS is balanced by the antioxidant action of non-enzymatic antioxidants, as well as antioxidant defense enzymes.

Catalase (CAT; OMIM: 115500), is the most potent enzyme [7] that inducible by exposure to reactive species, particularly H_2O_2 [3]. Catalase is present in all aerobic cells. Catalase activity is likely to be affected by functional polymorphism of C-262 T (rs1001179) in the *CAT* gene. The C-262 T polymorphism in the promoter region of the *CAT* gene was found to be associated with altered catalase activity [7, 8]. Considering that CAT is one of the major enzymes involved in cellular detoxification [3, 7], several studies on the *CAT* C-262 T polymorphism associated with several types of multifactorial traits, including some types of cancers have been published [9–24].

Reduction in CAT activity may play a role in host response to oxidative stress and indeed variant T allele has been association with increased risk of breast cancer [9]. It is hypothesized that individuals with the lower expressing forms of the *CAT* C-262 T polymorphism may be more susceptible to the breast cancer risk. Therefore, to clarify the effect of this polymorphism on the risk of developing breast cancer, we carried out a case–control study and a meta-analysis of the literatures using published data up to the November 2013, to obtain more precise estimates of risk.

Materials and Methods

Case–Control Study

This case–control study consisted of 407 females with breast cancer that were recruited from chemotherapy department of Nemazi hospital in Shiraz (south-west of Iran). A total of 395 healthy female from population matched with patients according to age, as a control group. The mean age of the patients and the controls was 43.9±8.8 years and 45.2±10.7 years, respectively. Because Iranian population is one of the most heterogeneous populations [25, 26], we select our patients and controls from Persian (Caucasians) Muslims living in Shiraz. Informed consent was obtained from each subject before the study. This study was approved by the local ethics committee.

Blood samples were collected from the subject. Genomic DNA was extracted from whole blood samples. Genotypic analysis for the *CAT* C-262 T polymorphism was determined using the specific primers: 5′-CTG ATA ACC GGG AGC CCC GCC CTG GGT TCG GAT AT-3′ and 5′-CTA GGC AGG CCA AGA TTG GAA GCC CAA TGG-3′ as described previously [27]. The cycling conditions were: 95°C for 15 min, 35 three-step cycles (94°C, 1 min; 68°C, 1 min; 72°C, 1 min), followed by 72°C for 15 min. PCR products were digested by restriction endonuclease *EcoR V* for 16 h at 37°C. The products were electrophoresed on 1.5 % agarose gel. The gels were stained with ethidium bromide and visualized by ultraviolet light. The C allele produced a 190 bp band, whereas the T allele digested by *EcoR V* and produced 157 and 33 bp bands.

For control group of the study, the observed frequencies of the *CAT* genotypes were assessed for Hardy-Weinberg equilibrium using the χ^2 statistic. The associations between the *CAT* C-262 T genotypes and risk of breast cancer were assessed by calculating odds ratios (ORs) and 95 % confidence intervals (CIs). Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) (version 11.5). A probability of $P<0.05$ was considered statistically significant.

Meta-Analysis

There are a few numbers of studies that have considered *CAT* C-262 T polymorphism in relation to breast cancer risk [9–14]. Studies published up to November 2013 with information of the *CAT* C-262 T polymorphism and breast cancer were identified using electronic databases, MEDLINE (National Library of Medicine, Washington, DC, USA), Scopus, Socolar, Academic Journals Databases, Scirus, DOAJ (Directory of Open Access Journals), Indian Science Abstract, Google Scholar, SAGE, Open J-Gate, High-Wire, J-STAGE, KoreaMed, and SID (Scientific Information Database). Search terms were “breast cancer”, “catalase” and ‘CAT”. We cross-referenced literature cited in research articles and checked review articles of breast cancer genetics, *CAT* polymorphism and cancer susceptibility genes for studies not otherwise identified. The meta-analysis was limited to published data in English language.

Articles selected for analysis were studies with case–control design and their primary references had no obvious

Table 1 Selected characteristics of participants of breast cancer study

Characteristics	Categories	Controls (n=395)	Cases (n=407)	P*
Age (years)	Mean±SD	43.9±8.8	45.2±10.7	0.06
Age at diagnosis (years)	Mean±SD	–	45.2±10.7	–
Age at menarche (years)	Mean±SD	13.3±1.6	13.4±1.6	0.58
Marital status	Married	371	325	
	Single	26	35	0.11
	Missing	0	47	
Menopausal status				
	Premenopausal	290	246	0.26
	Postmenopausal	98	100	
	Missing	9	61	
Cigarette smoking	Non-smokers	343	337	
	Smokers	52	63	0.30
	Missing	2	7	
FH**	Negative	373	383	0.006
	Positive	5	19	
	Missing	19	5	

*P associated with either *Student's t-test* or chi-square test and Fisher's exact test

**Family history of breast cancer in the first-degree relatives

Table 2 Genotypic distribution of the *CAT* C-262 T polymorphism among cases and controls

Subjects/Genotypes	Controls	Cases	OR	95 % CI	P-value
All subjects					
CC	240	261	1.0	–	–
CT	132	129	0.90	0.66–1.22	0.484
TT	23	17	0.68	0.35–1.30	0.245
CT+TT	155	146	0.86	0.65–1.15	0.325
Premenopausal					
CC	181	157	1.0	–	–
CT	89	76	0.98	0.67–1.43	0.935
TT	18	13	0.83	0.39–1.75	0.630
CT+TT	107	89	0.95	0.67–1.36	0.816
Postmenopausal					
CC	57	61	1.0	–	–
CT	38	37	0.91	0.51–1.62	0.749
TT	3	2	0.62	0.10–3.86	0.611
CT+TT	41	39	0.88	0.50–1.56	0.684

There is no linear trend for presence of 0, 1 and 2 the T allele (χ^2 =1.61, P=0.204) and risk of breast cancer

Table 3 Summary characteristic for all included studies in the meta-analysis

Study (year)	Ref.	Place	Source of control	Control			Case		
				CC	CT	TT	CC	CT	TT
Ahn et al., 2005[a]	9	USA	Population Based	679	335	42	614	349	45
Cebrian et al., 2006	10	UK	–	1,362	787	113	1,351	707	113
Quick et al., 2008[b]	11	USA	Population Based	97	10	1	34	13	0
Quick et al., 2008[c]	11	USA	Population Based	598	333	43	345	197	27
Li et al., 2009	12	USA	Population Based	303	167	23	295	176	26
Tsai et al., 2012	13	Taiwan	Population Based	202	22	0	225	35	0
Present study, 2014	–	Iran	Population Based	240	132	23	261	129	17

[a] Numbers of the CT and TT genotypes were calculated according to the Hardy-Weinberg equilibrium

[b] Participants were non-Caucasians

[c] Participants were Caucasians

overlap of cases with other studies. For each study, we abstracted the publication date, country where the study was conducted, control source, number of cases and controls, and ethnicity. Study of Quick et al., [11] reported two case–control studies based on the ethnicity of their participants. Considering that the study of McCullough et al., [14] showed obvious overlap of subjects with the study of Ahn et al., [9], the study of McCullough et al., [14] was not included in the analysis. The application of these criteria yielded 7 case–control studies eligible for meta-analysis.

For control group of each study, the observed frequencies of the *CAT* genotypes were assessed for Hardy-Weinberg equilibrium using the χ^2 statistic. The chi-square-based Q statistic test was adopted to estimate the between-studies heterogeneity, and the heterogeneity was statistically significant if the *P* value is less than 0.05 [28]. The association was measured using random-effect or fixed-effect models according to the studies' heterogeneity. The fixed-effects method assumes no significant heterogeneity between the results of the individual studies being pooled, whereas, the random-effects method allows for such heterogeneity. The fixed-effects and random-effects methods were used by Mantel-Haenszel [29] and DerSimonian and Laird methods [28], respectively. The CC genotype was used as the baseline for calculation of ORs.

Results

The general characteristics of breast cancer patients and control group are summarized in Table 1. Family history significantly differed between cases and controls (P=0.006). However, smoking habit, marital status, menopausal status, age of menarche did not differ significantly between cases and controls (P>0.05).

Table 2 shows the genotypes of *CAT* C-262 T polymorphism in breast cancer cases and healthy controls. The genotypic frequencies of the control subjects did not show significant deviation from Hardy-Weinberg equilibrium (χ^2=0.72, df=1, P=0.395). Table 2 also shows the association between the *CAT* C-262 T polymorphism and breast cancer risk. The CT (OR=0.90, 95 % CI: 0.66–1.22, P=0.484) and TT (OR=0.68, 95 % CI: 0.35–1.30, P=0.245) genotypes were not associated with breast cancer risk compared to the CC

Table 4 Meta-analysis results for the *CAT* C-262 T polymorphism and breast cancer risk

Comparisons	No of studies	Q statistic	OR	95 % CI	*P*-value
All Studies					
CT *vs* CC	7	14.90*	1.01	0.92–1.09	0.862
TT vs CC	7	2.57	1.03	0.85–1.24	0.770
CT+TT *vs* CC	7	14.58*	1.01	0.93–1.09	0.792
T *vs* C	7	12.88*	1.01	0.94–1.09	0.725
All studies after excluding smallest study					
CT *vs* CC	6	7.01	0.99	0.92–1.08	0.934
TT *vs* CC	6	2.21	1.03	0.85–1.24	0.854
CT+TT *vs* CC	6	7.46	1.01	0.92–1.08	0.977
T *vs* C	6	6.95	1.00	0.94–1.07	0.868

*There is heterogeneity between studies P<0.05

genotype. Also, there is no linear trend for presence of the 0, 1, and 2 the T allele and risk of breast cancer (χ^2=1.61, P=0.204). The same results revealed when the participants were stratified by the menopausal status (Table 2).

We identified 7 eligible studies [9–13, present study], including 10,471 subjects (4,959 patients, and 5,512 healthy controls) in relation to the *CAT* C-262 T polymorphism and breast cancer risk, which are summarized in Table 2. The numbers in the case–control studies varied considerably (range 155 to 4,433 individuals). The control groups were at Hardy-Weinberg equilibrium (Table 3). Including all studies, there was significant heterogeneity between studies (Table 4). The overall ORs of the breast cancer risk were not associated with the CT (Q-statistic=14.90, df=6, P<0.05; OR=1.01, 95 % CI: 0.92–1.09, P=0.862) and TT (Q-statistic=2.57, df=6, P>0.05; OR=1.03, 95 % CI: 0.85–1.24, P=0.770) genotypes. After excluding the smallest study (study of Quick et al., 2008 on non-Caucasian participants [11]), the heterogeneity between studies decreased dramatically. However, there was no association between polymorphism of *CAT* and risk of breast cancer (Table 4).

Discussion

In the present population-based case–control study, we found that although the risk of breast cancer in the CT and TT genotypes of *CAT* C-262 T polymorphism decreased compared with the CC genotype, the ORs were not reached to the statistically significant level (Table 2). One explanation for this finding is the relatively small sample size. In order to clarify the effect of this polymorphism on the risk of breast cancer, a meta-analysis using published studies was carried out.

Considering the role of oxidative stress in the breast carcinogenesis [1–5], function of CAT in cellular detoxification [3, 7], and functional polymorphism of C-262 T on the promoter of *CAT* gene [7–9], it is hypothesized that this polymorphism might be involved in alteration of breast cancer risk. However, our analysis did not support this hypothesis.

It have been reported that in peripheral blood mononuclear cells, the lower CAT activity was observed in the CT and TT genotypes as compared with the CC genotype during H_2O_2-induced oxidative stress [30]. On the other hand, interaction between genotypes of the C-262 T polymorphism of *CAT* and CAT activity under conditions of oxidative stress was reported [31].

The interaction between C-262 T polymorphism and environmental factors (e.g. diet) for enzyme activity of CAT was reported [7, 9]. Therefore, it is necessary that in future studies, participants were stratified particularly in relation to fruit and vegetable intake and supplement use.

Major limitation of the present meta-analysis study is the geographical distribution of the studies used in the analysis. There is only one study from Asian populations [13] and no study from African populations. It has been reported that there is significant interaction between ethnicity and susceptibility to cancers in relation to some polymorphisms [32–35]. Larger studies with detailed data on environmental factors (such as fruit and vegetable intake and supplement use) from different ethnic groups are needed, in order to investigating the interaction between environmental factors and the polymorphism of C-262 T *CAT*.

In conclusion, the present study suggested that there is no significant association between genetic polymorphism of C-262 T (rs1001179) in the catalase (*CAT*) gene and susceptibility to breast cancer.

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Conflict of Interest No competing interests are declared by any of the authors.

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