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ORIGINAL ARTICLE

Association between Genetic Polymorphisms in Superoxide Dismutase Gene Family and Risk of Gastric Cancer

Alireza Eftekhari[1] · Zahra Peivand[1] · Iraj Saadat[1] · Mostafa Saadat[1]

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Abstract

To determine the association between the *SOD1* (Ins/Del), *SOD2* (rs2758339, rs5746136), and *SOD3* (rs2536512) polymorphisms and the risk of gastric cancer the present study performed. This is a case-control study, including 159 patients with gastric cancer and 242 healthy controls. All subjects were Persian Muslims living in Shiraz (south west Iran). Frequency matching by age and gender was performed. Genomic DNA was extracted from whole blood. Genotypes of the study polymorphism were determined using polymerase chain reaction based methods. The *SOD1* Ins/Del and *SOD3* rs2536512 polymorphisms did not appear to have relationship with gastric cancer risk. Both *SOD2* polymorphisms (rs2758339, rs5746136) showed significant association with the risk of gastric cancer, under assumption that the variant alleles act as dominant alleles. There was significant association between smoking habit and the risk of gastric cancer (OR = 2.54, 95% CI = 1.61–4.02, $P < 0.001$). Smoker individuals having two putative high-risk genotypes showed elevated risk of gastric cancer compared with nonsmokers without high-risk genotypes, (OR = 5.75, 95% CI = 1.59–20.6, $P = 0.007$). Assuming that smoking habit and the genotypes are independent risk factors, there was a significant linear trend for the numbers of risk factors and gastric cancer risk ($\chi^2 = 22.9$, $P < 0.001$). This study indicates that the *SOD2* polymorphism (rs2758339, rs5746136) is associated with increased risk of gastric cancer, especially in smoker individuals.

Keywords Gastric cancer · *SOD1* · *SOD2* · *SOD3* · Polymorphism

Introduction

Studies have indicated that gastric cancer has heritability [1, 2] it means that several environmental and genetic predisposing factors are involved in its pathogenesis [3, 4]. Although the pathogenesis of gastric cancer has not been understood completely, it is well established that oxidative stress implicated in its development [5]. Reactive oxygen species (ROSs) are unstable metabolite of oxygen and leads to oxidation of many macromolecules, including DNA [6]. Oxidative stress can occur due to an increased production of ROSs and/or a reduction in cellular antioxidant capacity [7].

Enzymatic and non-enzymatic antioxidant systems protect cells and body from the ROSs toxicity [8]. The enzymatic system contains several antioxidant enzyme families such as superoxide dismutases family (SODs; EC 1.15.1.1) [8, 9]. The SOD converts superoxide into hydrogen peroxide and is the most important defense system against ROS. It is classified into three distinct isoforms in mammals. The SOD1 (OMIM: 147450), SOD2 (OMIM: 147460), and SOD3 (OMIM: 185490) are cytosolic, mitochondrial and extracellular enzymes, respectively. The SOD1 and SOD3 enzymes contain copper and zinc and the SOD2 contains manganese in their active sites [9, 10]. Several polymorphisms were reported in the *SOD1*, *SOD2*, and *SOD3*. A 50 bp Insertion/Deletion (Ins/Del) genetic polymorphism has been reported in the promoter region of *SOD1* (1684 bp upstream of the ATG start codon) [11]. This polymorphism alters the *SOD1* expression levels; the Del allele associated with the reduced *SOD1* mRNA level

Alireza Eftekhari and Zahra Peivand have equal contributions.

✉ Iraj Saadat
isaadat@shirazu.ac.ir

✉ Mostafa Saadat
saadat@shirazu.ac.ir; msaadat41@yahoo.com

Alireza Eftekhari
alireza_efi72tan@yahoo.com

Zahra Peivand
Peivand.zahra@yahoo.com

[1] Department of Biology, College of Sciences, Shiraz University, Shiraz 71467-13565, Iran

[12]. The polymorphisms of rs5746136 and rs2758339 have been reported for the *SOD2*. These polymorphisms are located in the vicinity of SP1 and NF-κB transcription element sequences [13] and glucocorticoid receptor binding site [14]. The rs2536512 polymorphism of *SOD3* results in substitution of alanine by threonine [15]. Therefore, it seems that the above-mentioned polymorphisms are functional.

Losses of 4p and 21q [16–20] and gains of 6q are non-randomly reported in gastric cancer [21, 22]. Genome scan showed that the human 21q chromosome segment is associated with the risk of gastric cancer [23]. The high expression levels of the *SOD2* have been reported in gastric cancer [24]. On the other hand, the genes encoding *SOD1*, *SOD2*, and *SOD3* were assigned to human chromosomes 21q22, 6q25.3 and 4p15.2, respectively [25–27]. Taken together, it is suggested that genetic polymorphisms of the SOD family might be associated with the risk of gastric cancer.

In a few studies, the association of *SOD1*, *SOD2*, and *SOD3* polymorphisms with several types of cancers have been studied [14, 29–31]. Considering that there is no published data on the association between the *SOD1* (Ins/Del), *SOD2* (rs5746136, rs2758339), and *SOD3* (rs2536512) polymorphisms and the risk of gastric cancer, the present study was carried out.

Materials and Methods

Study Subjects

The present case-control study included a total of 159 (103 males, 56 females) patients with gastric cancer who were referred to chemotherapy department of Namazi hospital (Shiraz, south-west Iran) and 242 (167 males, 75 females) normal control subjects. The mean age (SD) of the patients and the controls were 57.3 (12.8) and 56.7 (9.8) years, respectively. There was no significant difference between case and control groups. Iranian population is one of the most heterogeneous populations [32–34]. To control for such variation and have a more homogeneous groups, we selected our patients and controls from the same ethnical religious group (Persian Muslims living in Fars province, south-west Iran).

This study was approved by the Shiraz University ethics committee. Informed consent was obtained from all participants before the study. This work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for Ethical Principles for Medical Research Involving Human Subjects.

DNA Extraction and Genotyping Analysis

Blood samples with EDTA anticoagulant were obtained from patient and control groups and stored at −20 °C until use. Genomic DNA from whole blood was isolated by standard procedure. Genotypes of the study polymorphisms were detected using PCR based methods, as described previously [11, 13–15]. It should be noted that we failed to successfully determine the rs2758339 polymorphism in 4 participants, explaining the variation in the total number of samples listed in Table 1.

Statistical Analysis

A Chi-square test was performed for each polymorphism to determine if the control participants demonstrated Hardy–Weinberg equilibrium. The associations between the genotypes of study polymorphisms and the risk of gastric cancer were expressed as odds ratios (ORs). Ninety-five percent confidence intervals for the ORs (95% CI) were reported.

Smoking habit is one of the important risk factor for gastric cancer [4, 28]. Therefore, the participants were stratified by their smoking habit and the data were reanalyzed. Data on smoking status in the control and gastric cancer subjects were missed for 21 and 6 participants, respectively. In order to study the potential influence of the smoking on gastric cancer risk as well as the risk associated with the *SOD2* polymorphisms, the "sensitivity analysis" was used. For this analysis we assumed that 50% of the missing cases were smokers.

Table 1 Distributions of *SOD1* (Ins/Del), *SOD2* (rs2758339, rs5746136) and *SOD3* (rs2536512) polymorphisms with the risk of gastric cancer

Genotype	Gastric cancer	Controls	OR	95% CI	P
SOD1 Ins/Del					
Ins/Ins	115	190	1.0	–	–
Ins/Del	39	46	1.40	0.86–2.27	0.174
Del/Del	5	6	1.37	0.41–4.61	0.604
Ins/Del + Del/Del	44	52	1.39	0.87–2.22	0.157
*SOD2 rs*2758339					
CC	12	34	1.0	–	–
AC	90	117	2.17	1.06–4.44	0.032
AA	57	87	1.85	0.88–3.88	0.100
AC + AA	147	204	2.04	1.02–4.07	0.043
*SOD2 rs*5746136					
GG	43	94	1.0	–	–
GA	83	107	1.69	1.07–2.68	0.025
AA	33	41	1.76	0.98–3.15	0.058
GA + AA	116	148	1.71	1.11–2.64	0.015
*SOD3 rs*2536512					
GG	29	50	1.0	–	–
AG	74	105	1.21	0.70–2.09	0.484
AA	56	87	1.11	0.62–1.95	0.719
AG + AA	130	192	1.16	0.70–1.94	0.551

Table 2 Comparison of the haplotypes of the rs2758339 and rs5746136 *SOD2* polymorphisms in gastric cancer patients and healthy controls

Haplotypes		Controls	Cases	OR	95% CI	P
rs2758339	rs5746136					
C	G	174	101	1.0	–	–
A	G	115	69	1.03	0.70–1.52	0.867
A	A	176	134	1.31	0.94–1.82	0.110
C	A	11	14	2.19	0.95–5.01	0.063

The software SNPAlyze(TM) ver. 6 Standard (Dynacom Co, Ltd. Kanagawa, Japan) was used to evaluate the status of pair wise linkage disequilibrium for the studied polymorphisms. Statistical analyses were performed with SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL). The *P*-values of less than 0.05 were considered statistically significant.

Data Availability No additional data are available for this study.

Results and Discussion

Table 1 presents the genotypic and allelic frequencies of the genes encoding *SOD* family among gastric cancer patients and healthy controls. The observed genotypic frequencies of the study polymorphisms among control subjects were consistent with the expected values based on Hardy-Weinberg equilibrium (for the *SOD1* Ins/Del polymorphism: $\chi^2 = 2.36$, df = 1, $P = 0.123$; for the *SOD2* rs2758339 polymorphism: $\chi^2 = 0.28$, df = 1, $P = 0.594$; for the *SOD2* rs5746136 polymorphism: $\chi^2 = 1.22$, df = 1, $P = 0.268$; for the *SOD3* rs2536512 polymorphism: $\chi^2 = 3.00$, df = 1, $P = 0.082$).

The *SOD1* Ins/Del and *SOD3* rs2536512 polymorphisms did not appear to have relationship with the risk of gastric cancer (Table 1). There is no study on relationship between *SOD1* Ins/Del polymorphism and cancer risk. However, there is only one study on the association between the *SOD3* rs2536512 polymorphism and breast cancer risk, which is inconsistent with our present findings [31]. Both *SOD2* polymorphisms showed significant association with the risk of gastric cancer, under assumption that the variant alleles act as dominant alleles (Table 1). A few studies were published in relation to association between these polymorphisms and risk of other types of cancer revealed consistent results with our present findings [14, 29, 30].

A significant linkage disequilibrium was observed between the *SOD2* polymorphisms (for control group: D' = −0.8523, $r^2 = 0.2988$, $\chi^2 = 141.0$, $P < 0.001$; for gastric cancer group: D' = −0.7418, $r^2 = 0.2690$, $\chi^2 = 85.31$, $P < 0.001$). Considering that the CC and GG genotypes of the rs2758339 and rs5746136 polymorphisms, respectively, showed the lower risks for gastric cancer (Table 1), we used the CG haplotype as a reference. Statistical analysis showed that there was no significant association between the study haplotypes and the risk of gastric cancer (Table 2). This finding confirms the fact that both variant alleles of the *SOD2* polymorphisms act as dominant alleles.

In further analysis, we stratified the participants based on the recessive and dominant genotypes of the *SOD2* polymorphisms. The numbers of putative high-risk genotypes of the *SOD2* polymorphisms in gastric cancer and control groups were shown in Table 3. There was a significant linear trend for the numbers of putative high-risk genotypes and the risk of gastric cancer ($\chi^2 = 6.06$, $P = 0.014$).

The prevalence of smoker subjects among control and patient groups were 21.1% (out of 217 participants) and 40.5% (out of 153 participants), respectively. There was significant association between smoking habit and risk of gastric cancer (OR = 2.54, 95% CI = 1.61–4.02, $P < 0.001$). Tobacco smoke is one of the well known risk factor for development of gastric cancer [4, 28]. It has been reported that cigarette smoking

Table 3 Association between numbers of putative high risk genotypes of the *SOD2* (rs2758339, rs5746136) polymorphisms stratified by the smoking status of the participants

Genotypes		Number of risk factors	Controls	Cases	OR	95% CI	P
rs2758339	rs5746136						
Non-smokers							
CC	GG	0	15	4	1.0	–	–
CA + AA	GG	1	52	18	1.29	0.38–4.42	0.677
CC	AG + AA	1	50	28	2.10	0.63–6.94	0.224
CA + AA	AG + AA	2	54	41	2.84	0.87–9.22	0.081
Smokers							
CC	GG	1	3	3	3.75	0.53–26.1	0.183
CA + AA	GG	2	16	16	3.75	1.01–13.7	0.047
CC	AG + AA	2	12	20	6.25	1.67–23.2	0.006
CA + AA	AG + AA	3	15	23	5.75	1.59–20.6	0.007

condensate influenced the expression of *SOD2* [35, 36]. We know that many of risk factors may act additively. In order to investigate the additive effects of smoking and the *SOD2* genotypes, participants were stratified by their smoking habit (Table 3). Smoker individuals having 2 putative high-risk genotypes showed higher-risk of gastric cancer compared with non-smokers with no high-risk genotypes (OR = 5.75, 95% CI = 1.59–20.6, $P = 0.007$). Assuming that smoking habit and the genotypes are risk factors, there was a significant linear trend for the numbers of risk factors and gastric cancer risk ($\chi^2 = 22.9$, $P < 0.001$), indicating that smoking and the dominant genotypes of the *SOD2* polymorphisms act in an additive model. Considering that data on smoking status in 27 participants were missed, we carried out the "sensitivity analysis" under assumption that 50% of them were smokers. After sensitivity analysis the above-mentioned associations did not change.

The gene encoding *SOD2* was located on human chromosome 6q25 [27]. Interestingly, gain of 6q chromosome segment is non-randomly has been reported in gastric cancer [21, 22]. On the other hand, *SOD2* was highly expressed in gastric cancer [24]. Taken together, it is suggested that *SOD2* might be involved in the risk of gastric cancer. Both polymorphisms of the *SOD2* (rs2758339 and rs5746136) are located in the vicinity of SP1 and NF-κB transcription element sequences [13] and glucocorticoid receptor binding site [14]. Our present findings support the possible involvement of *SOD2* in the development of gastric cancer. It has been reported that cigarette smoke contains oxidant compounds able to generate superoxide and alter the expression of *SOD2* [35, 36], which confirmed by our present findings (additive effect of smoking and the dominant genotypes of the *SOD2* polymorphisms, Table 3).

Small sample size is the major limitation of the present study. Therefore, the present findings should be confirmed by other studies with larger sample size in other populations.

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Author Contributions Eftekhari A and Peivand Z contributed equally; also Saadat I and Saadat M contributed equally; Eftekhari A and Peivand Z contributed to carry out the survey, collecting the data, genotyping assays and statistical analysis; Saadat I and Saadat M contributed to developing the study protocol, statistical analysis, interpreting the data, and writing the manuscript.

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Compliance with Ethical Standards

Institutional Review Board This study was approved by the ethics committee of biology department of Shiraz University, Iran (ECBD-SU-9330535).

Informed Consent Written informed consent was obtained from all participants before study participation. All experiments and data comparisons were carried out in compliance with relevant laws and guidelines and in accordance with the ethical standards of the Declaration of Helsinki.

Conflict of Interest The authors declare that they have no conflicts of interest.

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