Int J Clin Exp Med 2015;8(9):14647-14655
www.ijcem.com /ISSN:1940-5901/IJCEM0012497

Review Article

Superoxide dismutase 2 gene and cancer risk: evidence from an updated meta-analysis

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Received July 7, 2015; Accepted September 6, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Superoxide dismutase, one of the antioxidant enzymes, plays an important role in defense against reactive oxygen species. Many previous studies reported the association between SOD2 polymorphism and the cancer risk but the results were divergent. Therefore, we performed a meta-analysis to investigate the association between SOD2 polymorphism and the cancer susceptibility. We searched in Electronic database including Pubmed, Embase, google of scholar, and Korean Studies Information Service System (KISS) for this meta-analysis. Odds ratio (OR), 95 confidence interval (CI), and *p* value were calculated to evaluate the relation between SOD2 polymorphism and risk of cancer using Comprehensive Meta-analysis software (Corporation, NJ, USA). The fifty-two studies including 26,865 cancer cases and 32,464 control subjects were analyzed for meta-analysis. Our meta-analysis revealed that SOD2 polymorphism statistically increased or decreased the susceptibility of cancer. In the present study, we could find that SOD2 polymorphism was related to the development of non-Hodgkin lymphoma, lung cancer, and colorectal cancer. It suggested that SOD2 polymorphism might be a candidate marker of cancer.

Keywords: SOD2, MNSOD, superoxide dismutase 2, polymorphism, cancer, meta-analysis

Introduction

Cancer is a worldwide leading cause of death and the burden is growing all over the world [1]. Most cancers are caused by 2~8 sequential alterations and about 95% of these mutations are single-base substitutions. And these mutations play an important role in a regulation of cellular processes such as cell fate determination, cell survival, and genome maintenance through various signaling pathways [2, 3].

Reactive oxygen species (ROS) are known to induce DNA damage which leads to genetic lesions that initiate mutagenic activity and tumorigenicity [4]. ROS increases the mutation rate within cells and promotes oncogenic transformation. DNA damage including oxidized bases, formation of DNA adducts and DNA strand breaks by ROS causes the genomic instability [5]. These effects of ROS could be countervailed by the antioxidant action of non enzymatic antioxidants or antioxidant enzymes [6].

The antioxidant enzymes including superoxide dismutases (SOD), catalase (CAT) and glutathione peroxidases (GPX) are the most importantly involved in the damage by ROS [7]. Thus, genetic variations in the genes coding for these enzymes could cause the decreased or impaired regulation of the enzymatic activity and alter ROS detoxification [8].

Among the antioxidant enzymes, only SOD2 is within the mitochondria, which is a major site for ROS production [9]. The rs4880 polymorphism in exon2 of SOD2, located at position 16, is extensively studied, which changes the amino acid from alanine (Ala) to valine (Val) [10]. Val-variant could have a relation with decreased mRNA expression and stability, which have an important role in the import of SOD2 into the mitochondria [11].

Many previous studies studied the association between SOD2 polymorphism and cancer risks but the results are still controversial. After the meta-analysis in 2012 studied the association between single nucleotide polymorphisms of antioxidant enzymes and cancer risk [9], more studies have reported the relation between SOD2 polymorphism and more various cancer risks. Therefore, the aim of this meta-analysis

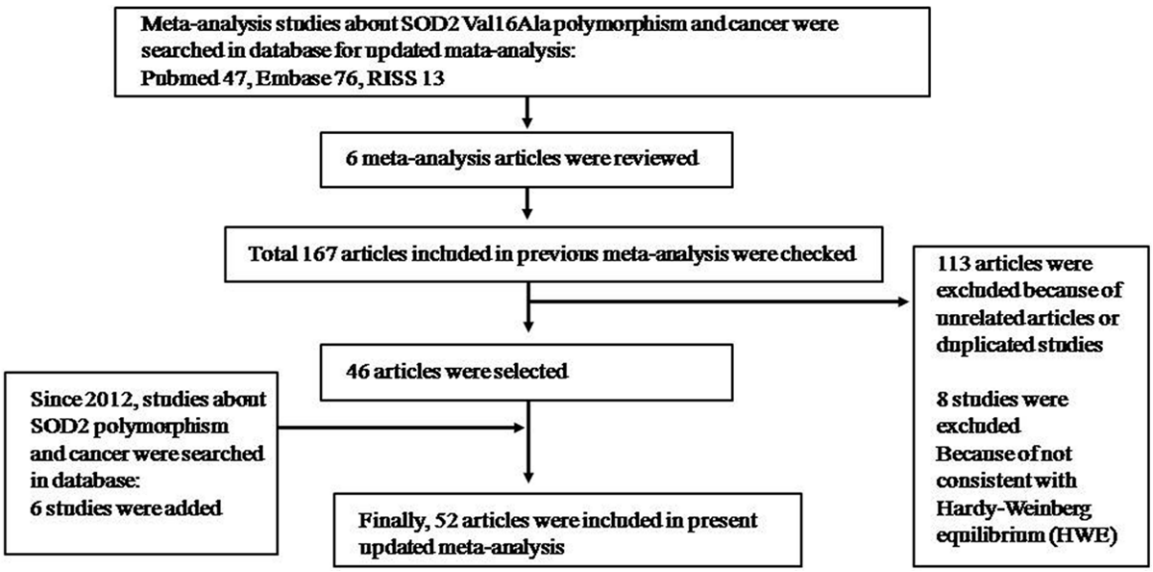

Figure 1. Flow chart to search eligible articles.

was to update previous meta-analysis and to evaluate the association of SOD2 polymorphism and various cancers risks.

Materials and methods

Search strategy

We searched studies in electronic database including Pubmed, Embase, google of scholar, and Korean Studies Information Service System (KISS) up to April 2015 to select suitable studies about SOD2 polymorphism and cancer. Meta-analysis study about SOD2 polymorphism and the association study between SOD2 polymorphism and risk of cancer were searched. The search keywords were "Superoxide Dismutase 2", "SOD2", "MNSOD", "Ala-9Val" or "Val16Ala", AND "polymorphism", "polymorphisms", or "variant" AND "cancer or carcinoma", or "meta analysis". The titles and abstracts were screened and full-text articles were examined.

Inclusion criteria and data extraction

Inclusion criteria were following: (1) assessed the relation between the SOD2 polymorphism and cancer; (2) compared cancer with control; (3) provided genotype and allele distributions of SOD2 polymorphism. The data of first author's name, published year, cancer type, country, ethnicity, sample size of cancer and control, and genotype frequencies of SOD2 polymorphism in cancer and control were gained from the final selected studies. The allele distributions were calculated from genotype distributions.

Statistical analysis

All included studies were tested to evaluate Hardy-Weinberg equilibrium (HWE) using the Chi-square test. Comprehensive Meta-analysis software (Corporation, NJ, USA) was used to perform meta-analysis. To evaluate the relation between risk of cancer and SOD2 polymorphism, the pooled *p* value, OR, and 95% CI were calculated. Sensitivity analysis was performed to determine the influence of each study on the final results. I^2 test was performed to evaluate the heterogeneity and the random effects model or the fixed effects model was selected based on the heterogeneity. OR with the corresponding 95% CI was calculated for the dominant model (C/C+C/G genotypes *vs*. G/G genotype) and recessive model (C/C *vs*. C/G+G/G genotypes), and allele (C vs. T), respectively. The $P<0.05$ was considered to be statistically significant. Begg's funnel plot and Egger's test were used to evaluate publication bias.

Results

This present meta-analysis was performed to examine the association between SOD2 polymorphism and various cancer risks. We searched the genetic data in various electronic

Table 1. Overall analysis between SOD2 polymorphism and risk of cancer

Cancers	Heterogeneity		Model	OR (95% CI)	P
	p	I-squared			
T vs. C					
All cancers	<0.001	64.457	Random	0.958 (0.916-1.003)	0.064
Breast cancer	0.141	28.863	Fixed	0.991 (0.950-1.034)	0.670
Prostate cancer	0.038	49.245	Random	0.940 (0.857-1.031)	0.191
Lung	0.048	58.188	Random	1.089 (0.947-1.252)	0.233
Bladder	0.134	50.299	Fixed	1.129 (0.971-1.312)	0.115
Non-Hodgkin lymphoma	0.945	<0.001	Fixed	0.919 (0.845-0.999)	0.047
Esophageal	0.011	84.372	Random	1.065 (0.648-1.750)	0.805
Colorectal Cancer	0.561	<0.001	Fixed	0.955 (0.893-1.020)	0.169
T/T *vs.* T/C+C/C					
All cancers	<0.001	52.398	Random	1.055 (0.993-1.121)	0.084
Breast cancer	0.188	24.042	Fixed	1.016 (0.952-1.085)	0.633
Prostate cancer	0.323	13.021	Fixed	1.089 (0.989-1.199)	0.083
Lung cancer	0.008	68.100	Random	0.969 (0.774-1.213)	0.782
Bladder cancer	0.057	65.148	Fixed	0.803 (0.644-1.002)	0.052
Non-Hodgkin lymphoma	0.663	<0.001	Fixed	1.077 (0.938-1.236)	0.291
Esophageal cancer	0.162	48.747	Fixed	1.040 (0.765-1.415)	0.802
Colorectal cancer	0.705	<0.001	Fixed	1.090 (0.979-1.213)	0.114
T/T+T/C vs. C/C					
All cancers	<0.001	54.921	Random	1.047 (0.976-1.123)	0.200
Breast cancer	0.061	39.025	Fixed	1.009 (0.937-1.087)	0.809
Prostate cancer	0.066	43.839	Fixed	1.058 (0.959-1.167)	0.261
Lung cancer	0.192	34.374	Fixed	0.838 (0.737-0.953)	0.007
Bladder cancer	0.714	<0.001	Fixed	0.948 (0.728-1.233)	0.690
Non-Hodgkin lymphoma	0.878	<0.001	Fixed	1.166 (1.017-1.336)	0.028
Esophageal cancer	0.008	85.785	Random	0.893 (0.398-2.004)	0.784
Colorectal cancer	0.553	<0.001	Fixed	1.038 (0.931-1.157)	0.505

databases and **Figure 1** showed the search strategy. We examined the 167 articles and 113 articles were omitted because they were unrelated or duplicated. Among them, 8 studies were excluded because of inconsistency with HWE. After including 46 articles, we supplemented 6 studies about SOD2 polymorphism since 2012. Finally, a total of 52 genetic studies about SOD2 polymorphism and cancer were included in this study (Supplementary Table 1) [12-59]. The total 59,329 individuals comprised of 26,865 cancer patients and 32,464 control subjects. The types of cancers were including breast (15 articles), prostate (10 articles), lung (6 articles), non-Hodgkin lymphoma (3 articles), bladder (2 articles), esophageal (2 articles), colorectal (6 articles) cancer, and so on.

As shown in **Table 1**, statistically significant associations between SOD2 polymorphism and several cancer risk were found in allele (T vs. C) model of non-Hodgkin lymphoma (OR =0.919, 95% CI =0.845-0.999), P=0.047) and recessive (T/T+T/C genotypes *vs.* C/C genotype) model of lung cancer (OR=0.838, 95% CI =0.737-0.953, P=0.007) and non-Hodgkin lymphoma (OR=1.166, 95% CI=1.017-1.336, P= 0.028). **Tables 2**, **3** show the results of meta-analysis of relation between SOD2 polymorphism and risk of cancer according to ethnicity. No association was found in Asian population and only dominant model of colorectal cancer in Caucasian population showed a significant association (OR=1.133, 95% CI=1.005-1.277, P=0.041). No publication bias was found but results of recessive model of lung cancer and non-Hodgkin lymphoma in all population and dominant model of colorectal cancer in Caucasian population were influenced by some studies according to sensitivity analysis.

Table 2. Overall analysis between SOD2 polymorphism and risk of cancer in Asian

Cancers	Comparison	Heterogeneity		Model	OR (95% CI)	P
		p	I-squared			
All cancers	T vs. C	<0.001	82.586	Random	0.807 (0.620-1.051)	0.112
	T/T vs. T/C+C/C	<0.001	74.574	Random	1.221 (0.966-1.543)	0.095
	T/T+T/C vs. C/C	0.014	60.299	Random	1.982 (0.958-4.102)	0.065
Breast cancer	T vs. C	0.797	<0.001	Fixed	0.965 (0.844-1.105)	0.609
	T/T vs. T/C+C/C	0.844	<0.001	Fixed	1.010 (0.868-1.175)	0.897
	T/T+T/C vs. C/C	0.700	<0.001	Fixed	1.384 (0.869-2.204)	0.171
Lung cancer	T *vs.* C	0.861	<0.001	Fixed	1.155 (0.847-1.574)	0.363
	T/T vs. T/C+C/C	0.390	<0.001	Fixed	1.024 (0.791-1.327)	0.855
	T/T+T/C vs. C/C	0.044	75.440	Random	0.484 (0.012-19.371)	0.700

Table 3. Overall analysis between SOD2 polymorphism and risk of cancer in Caucasian

Cancers	Comparison	Heterogeneity		Model	OR (95% CI)	P
		p	I-squared			
All cancers	T vs. C	0.000	60.561	Random	0.962 (0.908-1.018)	0.181
	T/T vs. T/C+C/C	0.005	46.487	Random	1.050 (0.970-1.137)	0.227
	T/T+T/C vs. C/C	0.000	59.502	Random	1.058 (0.964-1.161)	0.238
Breast cancer	T vs. C	0.094	39.597	Fixed	0.977 (0.927-1.031)	0.401
	T/T vs. T/C+C/C	0.426	1.392	Fixed	1.060 (0.971-1.156)	0.193
	T/T+T/C vs. C/C	0.016	55.780	Random	1.018 (0.875-1.184)	0.819
Prostate cancer	T *vs.* C	0.117	49.027	Fixed	0.926 (0.849-1.01)	0.084
	T/T vs. T/C+C/C	0.253	26.423	Fixed	1.110 (0.964-1.279)	0.148
	T/T+T/C vs. C/C	0.190	36.980	Fixed	1.105 (0.957-1.275)	0.173
Lung cancer	T *vs.* C	0.003	88.349	Random	0.997 (0.701-1.418)	0.987
	T/T vs. T/C+C/C	0.001	91.226	Random	0.923 (0.784-1.087)	0.335
	T/T+T/C vs. C/C	0.187	42.632	Fixed	0.861 (0.728-1.020)	0.083
Esophageal cancer	T vs. C	0.011	84.372	Fixed	1.065 (0.648-1.750)	0.805
	T/T vs. T/C+C/C	0.162	48.747	Fixed	1.040 (0.765-1.415)	0.802
	T/T+T/C vs. C/C	0.008	85.785	Random	0.893 (0.398-2.004)	0.784
Colorectal cancer	T vs. C	0.719	0.000	Fixed	0.931 (0.865-1.001)	0.055
	T/T vs. T/C+C/C	0.872	0.000	Fixed	1.133 (1.005-1.277)	0.041
	T/T+T/C vs. C/C	0.661	0.000	Fixed	1.068 (0.948-1.204)	0.276

Discussion

SOD plays an important role in protecting the organism against the damaging effects of the superoxide radical through converting it to hydrogen peroxide [60]. SOD2, one of the SOD family and called manganese (MN) SOD, contains an active site that has manganese as a transition metals for rapid electron exchange and is located in mitochondria. The mitochondria plays a key role in producing ROS [9]. The rs4880 polymorphism in SOD2 is a missense mutation that a single nucleotide change (from T to C) results in an amino acid change (from valine to alanine) (http://www.ncbi.nlm.nih.gov/). In Val-variant, impaired cotranslational import is observed, and that causes the slower mitochondrial import, lower levels of the mature exogenous protein, lower SOD2 activity and decreased mRNA expression and stability than Ala-variant [11]. It is well-known that ROS production could be a leading mediator in initiation, progression, and development of tumor [4], and SOD2 rs4880 polymorphism is closely associated with the function of SOD2. But results of previous studies on the relation between the SOD2 rs4880 polymorphism and the development of various cancers were conflicting and contradictory.

Previous meta-analysis studies on the relation between SOD2 polymorphism and the breast cancer risk failed to verify the link [17, 61, 62]. And meta-analysis on the SOD2 polymorphism and the risk of colorectal cancer [63] shows no statistically significant association. But lung cancer was significantly associated with SOD2 polymorphism [64]. Except for these, association of SOD2 with prostate cancer (in Caucasian) [65] and no association with bladder cancer [66] also were reported.

In our study, present meta-analysis includes 26,865 cancer cases and 32,464 controls. We could not find the statistically significant association between the SOD2 polymorphism and overall cancer risk in all models. In subgroup analyses by cancer types, the significant associations between the *SOD2* polymorphism and lung cancer (recessive model T/T+T/C vs. C/C: P=0.007, OR=0.838, 95% CI=0.737-0.953) and non-Hodgkin lymphoma (allele T vs. C: P=0.047, OR=0.919, 95% CI=0.845-0.999; recessive model T/T+T/C vs. C/C: P=0.028, OR=1.166, 95% CI=1.017-1.336) were detected. But in case of meta-analysis on breast cancer, lung cancer, prostate cancer, bladder cancer, and lymphoma, no associations were found. Some of these results are in accordance with previous studies. As describe above, previous meta-analysis on bladder cancer showed no association [66]. The results from studies on breast cancer were similar to ours [61, 62]. Meta-analysis in 2013 reported the relation between SOD2 polymorphisms and increased risk of prostate and esophageal cancers, and decreased risk of lung cancer [67] and the results consists with our result.

In present study, we have collected previous studies on various cancer and SOD2 polymorphism but our study has some limitations. Our results showed the association between SOD2 polymorphism and overall cancer risks. However, we could not examine the ethnic distribution because most studies included Caucasian and many studies in United States included mixed ethnicity. There were too little studies on Asians or African to investigate the ethnic distribution of SOD2 polymorphism. And in spite of genetic importance, environmental factors also are key factor in the development of cancer. But we could not examine the environmental factors in this meta-analysis. Previous studies on pancreatic cancer [68], oral squamous cell carcinoma [59], brain tumor [53], gastric cancer [52], and malignant pleural mesothelioma (MPM) [41] found the statistically significant association with SOD2 polymorphism. But the number of the studies was so small that we cannot perform the subgroup meta-analysis. As mentioned above, our results showed no evidence of publication bias, but some results were influenced by included articles. The result that showed no publication bias and was not influenced was only allele model result on non-Hodgkin lymphoma in all population.

Despite some limitation, our results showed the statistically significance in allele and genotype distribution. And we could find the association between the SOD2 polymorphism and esophageal cancer. If more results on individual cancers are accumulated in further studies, the relation between SOD2 polymorphism and the development of various cancers would be clarified.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Characteristics of eligible studies in meta-analysis

First author	Year	Cancer type	Country	Ethnicity	Case/ control	Cases			Controls		
						Ser/Ser (C/C)	Ser/Cys (C/G)	Cys/Cys (G/G)	Ser/Ser (C/C)	Ser/Cys (C/G)	Cys/Cys (G/G)
Tamimi	2004	Breast	United States	ND	968/1205	255	468	245	297	612	296
Cai	2004	Breast	China	Asian	1125/1197	831	266	28	884	290	23
Millikan	2004	Breast	United States	African	760/677	259	372	129	196	357	124
Millikan (II)	2004	Breast	United States	Caucasian	1265/1135	273	681	311	266	586	283
Mitrunen	2001	Breast	Finland	Caucasian	479/482	124	255	100	153	231	98
Ambrosone	1999	Breast (premenopausal)	United States	Caucasian	114/110	16	53	45	25	62	23
Gaudet	2005	Breast	United States	Caucasian	1034/1084	253	511	270	264	539	281
Slanger	2006	Breast	Germany	Caucasian	614/1080	144	318	152	263	528	289
Cheng	2005	Breast	Taiwan	Asian	469/739	343	115	11	545	183	11
Egan	2003	Breast	United States	Mixed	470/497	102	250	118	130	240	127
Knight	2004	Breast	Canada	Caucasian	399/372	107	187	105	90	195	87
Bergman	2005	Breast	Sweden	Caucasian	118/174	33	73	12	43	88	43
Green	2002	Breast	United Kingdom	Caucasian	39/36	13	17	9	8	22	6
Eras-Erdogan	2009	Breast	Turkey	Caucasian	250/330	107	113	30	150	141	39
Meplan	2013	Breast	Denmark	Caucasian	939/958	228	485	226	237	494	227
Kang	2007	Prostate	United States	Caucasian	1150/1382	275	578	297	376	686	320
Kang (II)	2007	Prostate	United States	African	103/395	31	57	15	122	194	79
Choi	2008	Prostate	United States	Mixed	469/1279	119	245	105	327	635	317
Li	2005	Prostate	United States	Mixed	567/764	132	288	147	190	379	195
Mikhak	2008	Prostate	United States	Mixed	642/652	156	320	166	162	331	159
Woodson	2003	Prostate	Finland	Caucasian	199/191	43	98	58	49	102	40
Iguchi	2009	Prostate	United States	Mixed	187/175	41	86	60	40	96	39
Arsova-Sarafinovska	2008	Prostate	Macedonia	Caucasian	85/151	19	46	20	41	73	37
Ergen	2007	Prostate	Turkey	ND	50/50	19	25	6	32	18	0
Dluzniewski	2012	Prostate	United States	Caucasian	472/472	131	233	108	117	236	119
Wang	2001	Lung	United States	Caucasian	1101/1239	305	551	245	288	628	323
Liu	2004	Lung	United States	Mixed	935/1233	255	472	208	285	626	322
Lan	2004	Lung	China	Asian	119/112	93	23	3	81	30	1
Lin	2003	Lung	Taiwan	Asian	198/314	139	59		233	81	
Ho	2006	Lung	China	Asian	234/239	176	58	0	180	52	7
Zienolddiny	2008	Lung	Norway	Caucasian	319/375	74	175	70	119	178	78
Landi	2007	Malignant pleural mesothelioma (MPM)	Italy	Caucasian	80/349	16	27	37	98	170	81
Zhao	2012	Glioma	China	Asian	379/380	241	107	31	293	81	6
Ichmura	2004	Bladder	Japan	Asian	213/209	169	41	3	157	48	4

Hung	2004	Bladder	Italy	Caucasian	201/214	68	89	44	45	115	54
Lightfoot	2006	Non-Hodgkin lymphoma	UK & US	Caucasian	903/1388	211	463	229	358	713	317
Wang	2006	Non-Hodgkin lymphoma	United States	Mixed	1120/937	285	545	290	240	486	211
Farawela	2012	Non-Hodgkin lymphoma	Egypt	-	100/100	10	50	40	12	49	39
Johnatty	2007	Ovarian	Australia	-	543/1130	123	273	147	276	546	308
Han	2007	Skin	United States	-	773/833	184	402	187	196	425	212
di Martino	2007	Esophageal	GER & UK	Caucasian	484/93	128	234	122	20	39	34
Murphy	2007	Esophageal	Ireland	Caucasian	396/221	93	196	107	60	113	48
Yi	2010	Gastric	China	Asian	140/147	85	48	7	119	27	1
Rajaraman	2008	Brain	United States	Caucasian	414/451	129	162	123	122	220	109
Amr	2015	Bladder	Egypt	-	356/414	109	160	87	127	188	99
Funke	2009	Colorectal Cancer	Germany	Caucasian	623/603	136	321	166	146	294	163
Levine	2002	Colorectal Cancer	United States	Mixed	456/495	139	209	108	140	234	121
Meplan	2010	Colorectal Cancer	Czech	Caucasian	719/657	172	358	189	165	318	174
Kang	2007	Colorectal Cancer	United States	Caucasian	1150/1382	275	578	297	376	686	320
Kang (II)	2007	Colorectal Cancer	United States	African	103/395	31	57	15	122	194	79
Landi	2005	Colorectal Cancer	Spain	Caucasian	335/303	94	164	77	88	151	64
Liu	2014	Oral squamous cell carcinoma	China	Asian	362/358	272	83	7	296	61	1