Int J Clin Exp Pathol 2017;10(9):9527-9540
www.ijcep.com /ISSN:1936-2625/IJCEP0054932

Original Article

Association between glutathione peroxidase-1 (GPX1) Rs1050450 polymorphisms and cancer risk

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Received April 8, 2017; Accepted June 30, 2017; Epub September 1, 2017; Published September 15, 2017

Abstract: Glutathione peroxidase (GPX), one of the antioxidant enzymes, exerts a vital role in reducing oxidative damage. GPX1 Pro198Leu (rs1050450) polymorphism has been reported in the development of several cancers, while the results were inconsistent. We thus conducted this meta-analysis to identify the association between GPX1 (rs1050450) polymorphism and cancer risk. 52 eligible publications with 60 case-control studies were included, with 21,296 cancer patients and 30,346 controls. The results in total population suggested there was a significant association between GPX1 (rs1050450) polymorphism and cancer susceptibility in part genetic models (TT vs CT+CC: OR = 1.15, 95% CI = 1.01-1.32, P = 0.042; TT vs CC: OR = 1.15, 95% CI = 1.00-1.31, P = 0.044; T vs C: OR = 1.09, 95% CI = 1.01-1.17, P = 0.02). The stratified analysis by cancer types suggested a positive correlation between GPX1 (rs1050450) polymorphism and the development of bladder cancer (TT+CT vs CC: OR = 1.72, 95% CI = 1.09-2.70, P = 0.019; TT vs CT+CC: OR = 3.56, 95% CI = 1.42-8.94, P = 0.007; TT vs CC: OR = 3.75, 95% CI = 1.41-9.94, P = 0.008; T vs C: OR = 1.941, 95% CI = 1.17-3.22, P = 0.01) as well as head and neck cancer (TT vs CT+CC: OR = 2.19, 95% CI = 1.39-3.46, P = 0.001) and brain cancer (TT+CT vs CC: OR = 1.19, 95% CI = 1.03-1.37, P = 0.018). These results support that GPX1 (rs1050450) polymorphism might be a candidate marker for cancer risk with type-specific effects.

Keywords: Glutathione peroxidase-1, rs1050450, polymorphism, cancer, susceptibility

Introduction

Cancer is an increasingly leading cause of death and is considered as a severe health burden in both developing and developed countries [1]. A variety of underlying mechanisms have been confirmed to demonstrate the carcinogenesis process and imbalance of oxidative stress [2]. Oxidation has been proved to participate in quite a few pathogenic processes, including anti-infection process, aging, carcinogenesis, metastasis and angiogenesis [3].

During these processes, previous evidence has demonstrated that reactive oxygen species (ROS)-mediated oxidative damage played a critical role, which initiated a storm of free radical cascade and subsequently caused indirect damage to cellular component, leading to denaturing and dysfunction of proteins [4], saturation and structural modification of certain lipids and DNA strains breaking [5]. Because most of these damages were irreversible and fatal, oxidative stress might decrease the genome stability and thus increase the possibility of tumorgenesis.

Anti-oxidative system plays a key role in preventing catastrophic oxidative storm in our body and it works as a balanced cycle. With the consumption of reductive species, certain enzyme families recycle to restore these reductive active molecules. Glutathione peroxidase (GPX) family is one of those anti-oxidative enzyme families, among which GPX1, encoded by GPX1 gene in humans and locating on chromosome 3, is the most abundant one functioning in the detoxification of hydrogen peroxide [6].

Multiple single nucleotide polymorphisms (SNPs) have been identified in the DNA

sequences of GPX1gene, however, only the Pro198Leu (also known as rs1050450, noted in NCBI database as position 200 and it has also been recorded to at position 197) polymorphism has been extensively investigated. Previous studies have demonstrated the association between low level of circulating GPX1 and increased risk of cancer, which was found in several types of cancers including breast cancer [7, 8], lung cancer [9], prostate cancer [10], and colorectal cancer [11]. As with the presumption, GPX1 Pro198Leu (C>T) polymorphism affected GPX1 activity, which might further play an important role in cancer development. However, possible relationships between GPX1 polymorphism and cancer have been studied only in separate types of cancer with conflicting results. Thus, we conducted a comprehensive meta-analysis to explore the association of GPX1 Pro198Leu (rs1050450) polymorphism with risk for cancer and investigated each individual tumor in subgroup analysis.

Methods

Study selection

PubMed, Embase, Science Direct, and Cochrane Library were searched on October 17, 2016 using the mesh terms: "glutathione peroxidase1 or GPX1", "polymorphism or variant or mutation" and "cancer or carcinoma or malignancy". There was no language restriction. All searched results underwent abstract review and potentially eligible studies were reviewed through whole text. Additional potential eligible studies regarding this topic were identified through the references in retrieved articles.

Inclusion and exclusion criteria

In our meta-analysis, we used the following inclusion criteria: (1) case-control studies or cohort studies, (2) studies investigating the relationship between GPX1 (rs1050450) polymorphism and cancer risk, and (3) Odds ratio (OR) with 95% confidence interval (CI) being applied to assess the strength of association. Studies were excluded if they met the following criteria: (1) in vitro studies or review articles, (2) duplicated publications, and (3) reports with incomplete data. If studies used overlapped cases, only the study with the largest sample size was enrolled.

Data extraction

Two investigators extracted all data independently, and a consensus was reached prior to further process. For one publication with several cancer types, each type was treated separately. From each study, the following basic characteristics were extracted: first author's name, year of publication, country of origin, ethnicity of the study population, source of control groups (population-based or hospital-based controls), genotyping methods, total number of cancer cases and controls, and genotype distributions of cases and controls.

Statistical analysis

The following genotype contrasts were evaluated: dominate genetic model (CT+TT vs CC), recessive genetic model (TT vs CT+CC), homozygote comparison (TT vs CC), heterozygote comparison (CT vs CC), and allele comparison (T vs C). The association between GPX1 Pro198Leu polymorphism and cancer risk was measured using the odds ratio (OR) with 95% confidence interval (95% CI). The significance of the pooled OR was determined by the Z test and *P* value less than 0.05 indicated that the result was of statistical significance. In addition, subgroup analysis according to cancer types and ethnicity were performed. In terms of heterogeneity, $P<0.10$ or $I^2>50\%$ represented that heterogeneity existed in pooled ORs. When homogeneity was acceptable ($P\geq0.10$, $I^2\leq50\%$), a fixed-effects model was applied to secondary analysis; otherwise, a random-effects model was used [12, 13]. Publication bias was assessed by Begg's funnel plot and Egger's linear regression test. We also further performed sensitivity analysis to evaluate the stability of our results. All *P* values were two-sided. All analyses were performed using STATA 12.0 (STATA Corporation, College Station, TX).

Results

Characteristics of eligible studies

According to our searching strategy, a total of 52 publications with 60 case-control studies were included in this meta-analysis, with 21,296 cancer patients and 30,346 controls. The study selection process was shown in (**Figure 1**). The baseline characteristics of in-

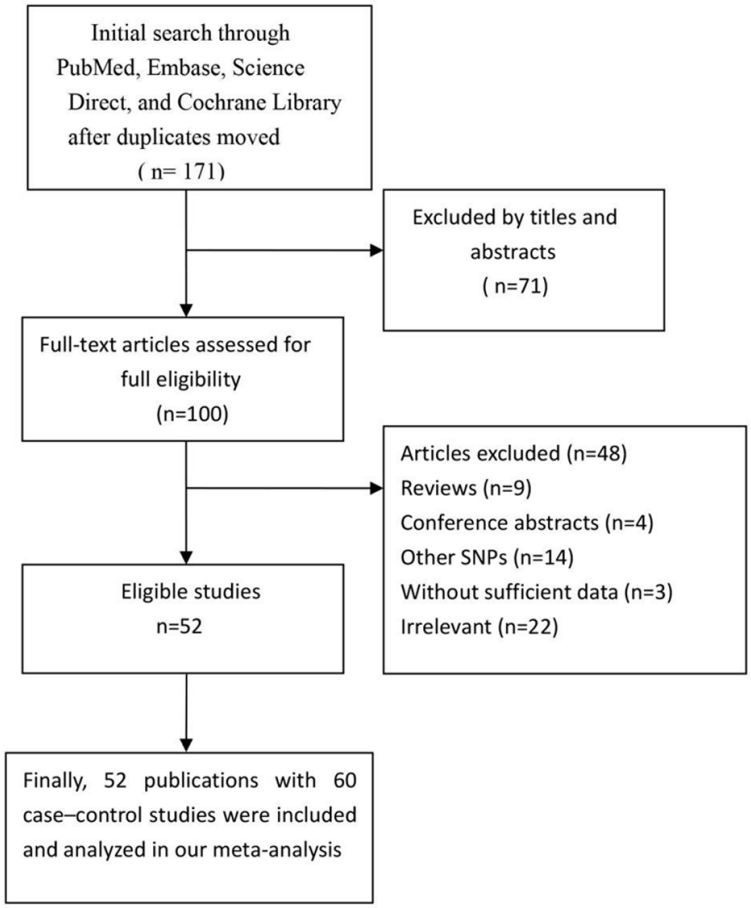

Figure 1. Flow chart of study selection in this meta-analysis.

cluded studies and genotype distributions were summarized in **Tables 1** and **2**. These 60 case-control studies were published from 2000 to 2016, among which there were 11 studies regarding prostate cancer, 10 studies on breast cancer, 6 studies about brain tumors (including acoustic neuroma, glioma, glioblastoma, multiforme, and meningioma), 6 studies on lung cancer, 5 studies regarding bladder cancer, 5 studies on colorectal cancer, 4 studies regarding skin cancer (including basal cell carcinoma, squamous cell carcinoma, and melanoma), 4 studies on non-Hodgkin lymphoma (NHL), 2 studies about hepatocellular carcinoma, 1 study on gastric cancer, 2 studies on myeloid leukemia, 3 studies regarding head and neck cancer (including laryngeal cancer and oral cavity cancer), and 1 study on pancreatic cancer. In all 52 included publications, 40 reports were analyzing Caucasian, 6 reports from Asian, 2 reports of African-Americans, and 12 reports of mixed ethnicity. Diverse genotyping methods were used in the included studies, various from polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan, general PCR, and Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI/TOF).

Pooled analysis

When all collected data were pooled into the meta-analysis, results showed that significant associations were found regarding to the following three genetic models (TT vs CT+CC: OR = 1.15, 95% CI = 1.01-1.32, P = 0.042; TT vs CC: OR = 1.15, 95% CI = 1.00-1.31, P = 0.044; T vs C: OR = 1.09, 95% CI = 1.01-1.17, P = 0.02), respectively (**Figure 2**). As for stratified analyses by cancer types, HWE and ethnicity, the pooled ORs for additive model and recessive model comparison suggested GPX1 (rs1050450) polymorphism was significantly associated with an increased risk of bladder cancer (TT+CT vs CC: OR = 1.72, 95% CI = 1.09-2.70, P = 0.019; TT vs CT+CC: OR = 3.56, 95% CI = 1.42-8.94, P = 0.007; TT vs CC: OR = 3.75, 95% CI = 1.41-9.94, P = 0.008; T vs C: OR = 1.94, 95% CI = 1.17-3.22, P = 0.01), and a relative association was found in head and neck cancer (TT vs CT+CC: OR = 2.19, 95% CI = 1.39-3.46, P = 0.001) and brain cancer (TT+CT vs CC: OR = 1.19, 95% CI = 1.03-1.37, P = 0.018). However, in prostate cancer, breast cancer, NHL, lung cancer and digestive system cancer, significant association was not found in any genetic model (all P>0.05). The association between GPX1 rs1050450 polymorphism and susceptibility to cancer was further proved in subgroup with controls consistent with Hardy-Weinberg equilibrium (TT+CT vs CC: OR = 1.07, 95% CI = 1.00-1.15, P = 0.041; T vs C: OR = 1.08, 95% CI = 1.01-1.15, P = 0.025). In subgroup analysis stratified by ethnicity, no associations were appreciated in Caucasian population (OR = 1.06, 95% CI = 0.98-1.15, P = 0.132), Asians (OR = 1.04, 95% CI = 0.47-2.30, P = 0.915), African-Americans (OR = 1.066, 95% CI

Table 1. Baseline characteristics of eligible studies

First Author	No.#	Year	Country	Ethnicity	Source of Controls	Sample	Quality Control	Control Health	Cancer Type	Case/Control	Genotyping method	HWE
Abe [14]		2011	USA	Caucasian	PB	Blood	NA	NA	Prostate cancer	356/745	PCR	Yes
Ahn [15]		2005	USA	Caucasian	PB	Blood	Yes	NA	Breast cancer	1038/1088	MALDI-TOF	Yes
Arsova-Sarafinovska [10]		2009	Macedonia	Caucasian	HB	Blood	NA	NA	Prostate cancer	82/123	PCR	Yes
Aynali [16]		2013	Turkey	Caucasian	HB	Blood	NA	Health	Laryngeal cancer	25/23	PCR	No
Banescu [17]		2014	Romania	Caucasian	HB	Blood	NA	Health	CML	168/321	PCR-RFLP	Yes
Banescu [18]		2016	Romania	Caucasian	HB	Blood	NA	Health	AML	102/303	PCR-RFLP	No
Bhatti [19]	1	2009	USA	Caucasian	HB	Blood	Yes	Unhealth	Glioma	327/457	TaqMan	NA
Bhatti [19]	2	2009	USA	Caucasian	HB	Blood	Yes	Unhealth	Glioblastoma multiforme	157/457	TaqMan	NA
Bhatti [19]	3	2009	USA	Caucasian	HB	Blood	Yes	Unhealth	Meningioma	121/457	TaqMan	NA
Cebrian [20]		2006	UK	Caucasian	PB	Blood	Yes	NA	Breast cancer	2293/2278	TaqMan	Yes
Cheng [21]		2011	USA	Mixed	PB	Blood	NA	NA	Prostate cancer	150/761	PCR	NA
Choi [22]	1	2007	USA	Caucasian	PB	Blood	Yes	Health	Prostate cancer	452/1221	MALDI-TOF	Yes
Choi [22]	2	2007	USA	African American	PB	Blood	Yes	Health	Prostate cancer	29/119	MALDI-TOF	Yes
Cox [23]		2004	USA	Caucasian	PB	Blood	NA	NA	Breast cancer	1323/1910	TaqMan	Yes
Erdem [24]		2012	Turkey	Caucasian	HB	Blood	NA	NA	Prostate cancer	33/91	PCR	Yes
Ermolenko [25]		2010	Russia	Caucasian	HB	Blood	NA	NA	Breast cancer	927/474	PCR TaqMan	Yes
Ezzikouri [26]		2010	France	Caucasian	HB	Blood	Yes	Health (163) HCV(59)	Hepatocellular carcinoma	96/222	PCR-RFLP	Yes
Goerlitz [27]		2011	Egypt	Caucasian	PB	NA	Yes	NA	Bladder Cancer	625/626	TaqMan	Yes
Hansen [28]		2005	Norway	Caucasian	PB	Blood	NA	NA	Colorectal cancer	166/397	PCR	Yes
Hansen [11]		2009	Denmark	Caucasian	PB	Blood	Yes	NA	Colorectal cancer	375/779	PCR	Yes
He [29]	1	2010	USA	Caucasian	PB	NA	NA	NA	Melanoma	207/809	TaqMan	Yes
He [29]	2	2010	USA	Caucasian	PB	NA	NA	NA	SCC	257/809	TaqMan	Yes
He [29]	3	2010	USA	Caucasian	PB	NA	NA	NA	BCC	281/809	TaqMan	Yes
Hu [8]		2003	Canada	African American	PB	Blood	Yes	NA	Breast cancer	79/517	PCR	Yes
Hu [30]		2004	USA	Mixed	HB	Blood	NA	NA	Head and neck cancer	133/517	PCR	Yes
Hu [31]		2005	USA	Mixed	HB	Blood	Yes	NA	Colon cancer	53/53	PCR	Yes
Ichimura [32]		2004	Japan	Asian	HB	Blood	Yes	Health	Bladder cancer	213/209	PCR-RFLP	Yes
Jablonska [33]		2015	Poland	Caucasian	HB	Blood	Yes	Health	Breast cancer	136/183	PCR	Yes
Karunasinghe [34]		2013	New Zealand	Mixed	HB	Blood	NA	Health	Prostate cancer	410/441	PCR	Yes
Knight [35]		2004	Canada	Caucasian	PB	Blood	NA	NA	Breast cancer	399/372	TaqMan	Yes
Kucukgergin [36]	1	2011	Turkey	Caucasian	HB	Blood	NA	Health	Prostate cancer	134/159	PCR-RFLP	Yes
Kucukgergin [37]	2	2012	Turkey	Caucasian	HB	Blood	NA	Health	Bladder cancer	157/224	PCR-RFLP	Yes
Lan [38]		2007	USA	Caucasian	PB	Blood	Yes	NA	NHL	449/520	PCR	No
Lee [39]		2006	Korea	Asian	HB	Blood	NA	NA	Lung cancer	200/200	PCR	Yes
Lightfoot [40]	1	2006	UK	Caucasian	PB	Blood	NA	NA	NHL-UK	620/762	TaqMan	Yes
Lightfoot [40]	2	2006	USA	Caucasian	PB	Blood	NA	NA	NHL-USA	308/684	TaqMan	Yes
Meplan [41]		2013	Denmark	Caucasian	PB	Blood	NA	NA	Breast cancer	933/959	PCR	Yes

Meplan [42]		2010	Czech	Caucasian	HB	Blood	Yes	Health	Colorectal cancer	681/637	PCR	No
Oskina NA [43]		2014	Russia	Caucasian	HB	Blood	NA	NA	Prostate cancer	361/326	TaqMan	Yes
Parlaktas [44]		2015	Turkey	Caucasian	HB	Blood	NA	Health	Prostate cancer	49/49	PCR	Yes
Paz-y-Miño [45]		2010	Ecuador	Mixed	PB	Blood	NA	NA	Bladder cancer	97/120	PCR-RFLP	Yes
Peters [46]		2008	USA	Mixed	PB	Blood	Yes	NA	Colorectal cancer	772/777	TaqMan	Yes
Raaschou-Nielsen [9]		2007	Denmark	Caucasian	PB	Blood	NA	NA	Lung cancer	432/798	PCR	Yes
Rajaraman [47]	1	2008	USA	Mixed	HB	Blood	Yes	Unhealth	Acoustic neuroma	69/494	TaqMan	Yes
Rajaraman [47]	2	2008	USA	Mixed	HB	Blood	Yes	Unhealth	Meningioma	134/494	TaqMan	Yes
Rajaraman [47]	3	2008	USA	Mixed	HB	Blood	Yes	Unhealth	Glioma	362/494	TaqMan	Yes
Ratnasinghe [48]		2000	Finland	Caucasian	PB	Blood	Yes	NA	Lung cancer	315/313	TaqMan	Yes
Ravn-Haren [7]		2006	Denmark	Caucasian	PB	Blood	Yes	NA	Breast cancer	377/377	PCR	Yes
Reszka [49]		2009	Poland	Caucasian	HB	Blood	NA	Health	Bladder cancer	33/47	PCR	Yes
Rosenberger [50]		2008	Germany	Caucasian	PB	Blood	Yes	NA	Lung cancer	186/207	MALDI-TOF	Yes
Skuladottir [51]		2005	Denmark	Caucasian	PB	Blood	NA	NA	Lung cancer	320/618	PCR	NA
Steinbrecher [52]		2010	Germany	Caucasian	PB	Blood	NA	Health	Prostate cancer	248/492	MALDI-TOF	Yes
Su [53]		2015	China	Asian	HB	Blood	Yes	NA	Hepatocellular carcinoma	434/480	PCR-RFLP	Yes
Tang [54]		2010	USA	Mixed	HB	Blood	NA	Health	Pancreatic cancer	575/648	PCR	Yes
Tsai [55]		2012	China	Asian	HB	Blood	Yes	Health	Breast cancer	260/224	PCR	No
Vogel [56]		2004	Denmark	Caucasian	PB	Blood	NA	NA	Basal Cell Carcinoma	317/317	PCR	Yes
Wang [57]		2008	China	Asian	HB	Blood	NA	NA	Gastric cancer	361/363	PCR-RFLP	Yes
Wang [58]		2006	USA	Mixed	PB	Blood	Yes	NA	NHL	740/636	TaqMan	Yes
Wu [59]		2010	China	Asian	HB	Blood	NA	Health	Oral cavity cancer	122/122	PCR	Yes
Yang [4]		2004	USA	Mixed	HB	Blood	Yes	NA	Lung cancer	237/234	PCR	No

[#]number of data separately reported by articles. HWE, Hardy-Weinberg equilibrium; MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PB, population-based; HB, hospital-based; NA, not available; CML, Chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; BCC, Basal cell carcinoma; SCC, Squamous cell carcinoma.

Table 2. Genotype frequency distribution of *GPX1* gene polymorphism

First Author	No.[#]	Ethnicity	Cancer Type	System	Case			Control			HWE
					TT	CC	CT	TT	CC	CT	
Abe [14]		Caucasian	Prostate cancer	Prostate cancer	169	137	50	340	314	91	Yes
Ahn [15]		Caucasian	Breast cancer	Breast cancer	472	456	110	523	453	112	Yes
Arsova-Sarafinovska [10]		Caucasian	Prostate cancer	Prostate cancer	54	17	11	57	47	19	Yes
Aynali [16]		Caucasian	Laryngeal cancer	Head and neck cancer	0	23	2	0	20	3	No
Banescu [17]		Caucasian	CML	Hematological malignancies	16	118	34	34	203	84	Yes
Banescu [18]		Caucasian	AML	Hematological malignancies	3	28	71	34	190	79	No
Bhatti [19]	1	Caucasian	Glioma	Brain cancer	158	169		236	221		NA
Bhatti [19]	2	Caucasian	Glioblastoma multiforme	Brain cancer	74	83		236	221		NA
Bhatti [19]	3	Caucasian	Meningioma	Brain cancer	55	66		236	221		NA

Cebrian [20]		Caucasian	Breast cancer	Breast cancer	1109	964	220	1066	993	219	Yes
Cheng [21]		Mixed	Prostate cancer	Prostate cancer	49	53		371	342		NA
Choi [22]	1	Caucasian	Prostate cancer	Prostate cancer	227	190	35	616	515	90	Yes
Choi [22]	2	African American	Prostate cancer	Prostate cancer	12	15	2	51	53	15	Yes
Cox [23]		Caucasian	Breast cancer	Breast cancer	581	515	133	774	694	161	Yes
Erdem [24]		Caucasian	Prostate cancer	Prostate cancer	11	17	5	40	41	10	Yes
Ermolenko [25]		Caucasian	Breast cancer	Breast cancer	452	375	100	192	230	52	Yes
Ezzikouri [26]		Caucasian	Hepatocellular carcinoma	Digestive system cancer	50	32	14	108	88	26	Yes
Goerlitz [27]		Caucasian	Bladder Cancer	Bladder Cancer	330	236	46	326	254	38	Yes
Hansen [28]	1	Caucasian	Colorectal cancer	Digestive system cancer	82	68	16	196	163	38	Yes
Hansen [11]	2	Caucasian	Colorectal cancer	Digestive system cancer	173	164	38	342	348	89	Yes
He [29]	1	Caucasian	Melanoma	Skin cancer	94	86	27	419	327	63	Yes
He [29]	2	Caucasian	SCC	Skin cancer	128	107	22	419	327	63	Yes
He [29]	3	Caucasian	BCC	Skin cancer	141	124	16	419	327	63	Yes
Hu [30]/		African American	Breast cancer	Breast cancer	36	25	18	244	209	64	Yes
Hu [30]		Mixed	Head and neck cancer	Head and neck cancer	69	30	34	244	209	64	Yes
Hu [31]		Mixes	Colon cancer	Digestive system cancer	33	15	5	24	26	3	Yes
Ichimura [32]		Asian	Bladder cancer	Bladder cancer	166	47	0	187	22	0	Yes
Jablonska [33]		Caucasian	Breast cancer	Breast cancer	73	51	12	75	85	23	Yes
Karunasinghe [34]		Mixed	Prostate cancer	Prostate cancer	122	110	30	216	186	33	Yes
Knight [35]		Caucasian	Breast cancer	Breast cancer	192	171	34	169	164	39	Yes
Kucukgergin [36]	1	Caucasian	Prostate cancer	Prostate cancer	32	62	40	78	61	20	Yes
Kucukgergin [37]	2	Caucasian	Bladder cancer	Bladder cancer	63	64	30	117	87	20	Yes
Lan [38]		Caucasian	NHL	Hematological malignancies	215	191	43	261	200	59	No
Lee [39]		Asian	Lung cancer	Lung cancer	116	84	0	154	46	0	Yes
Lightfoot [40]	1	Caucasian	NHL-UK	Hematological malignancies	311	259	43	438	268	55	Yes
Lightfoot [40]	2	Caucasian	NHL-USA	Hematological malignancies	142	128	38	335	283	65	Yes
Meplan [41]		Caucasian	Breast cancer	Breast cancer	465	396	72	503	370	86	Yes
Meplan [42]		Caucasian	Colorectal cancer	Digestive system cancer	354	306	21	355	259	23	No
Oskina NA [43]		Caucasian	Prostate cancer	Prostate cancer	183	146	32	153	132	41	Yes
Parlaktas [44]		Caucasian	Prostate cancer	Prostate cancer	27	16	6	24	17	8	Yes
Paz-y-Miño [45]		Mixed	Bladder cancer	Bladder cancer	28	19	50	73	42	5	Yes
Peters [46]		Mixed	Colorectal cancer	Digestive system cancer	351	288	77	355	331	57	Yes
Raaschou-Nielsen [9]		Caucasian	Lung cancer	Lung cancer	209	184	39	348	358	92	Yes
Rajaraman [47]	1	Mixed	Acoustic neuroma	Brain cancer	28	30	7	236	178	46	Yes
Rajaraman [47]	2	Mixed	Meningioma	Brain cancer	57	56	10	236	178	46	Yes
Rajaraman [47]	3	Mixed	Glioma	Brain cancer	165	140	35	236	178	46	Yes

Ratnasinghe [48]	Caucasian	Lung cancer	Lung cancer	91	157	67	132	135	46	Yes
Ravn-Haren [7]	Caucasian	Breast cancer	Breast cancer	176	168	33	205	136	36	Yes
Reszka [49]	Caucasian	Bladder cancer	Bladder cancer	13	15	5	27	18	1	Yes
Rosenberger [50]	Caucasian	Lung cancer	Lung cancer	114	63	9	97	89	21	Yes
Skuladottir [51]	Caucasian	Lung cancer	Lung cancer	50	69		172	185		NA
Steinbrecher [52]	Caucasian	Prostate cancer	Prostate cancer	123	108	16	264	181	42	Yes
Su [53]	Asian	Hepatocellular carcinoma	Digestive system cancer	371	19	0	454	27	0	Yes
Tang [54]	Mixed	Pancreatic cancer	Digestive system cancer	263	240	49	316	242	58	Yes
Tsai [55]	Asian	Breast cancer	Breast cancer	247	13	0	166	58	0	No
Vogel [56]	Caucasian	Basal Cell Carcinoma	Skin cancer	150	136	31	151	139	27	Yes
Wang [57]	Asian	Gastric cancer	Digestive system cancer	315	44	2	326	35	2	Yes
Wang [58]	Mixed	NHL	Hematological malignancies	360	310	70	291	284	61	Yes
Wu [59]	Asian	Oral cavity cancer	Head and neck cancer	108	12	0	112	10	0	Yes
Yang [4]	Mixed	Lung cancer	Lung cancer	111	98	20	114	85	29	No

[#]number of data separately reported by articles. HWE, Hardy-Weinberg equilibrium; CML, Chronic myeloid leukemia; AML, Acute myeloid leukemia; NHL, non-Hodgkin lymphoma; BCC, Basal cell carcinoma; SCC, Squamous cell carcinoma.

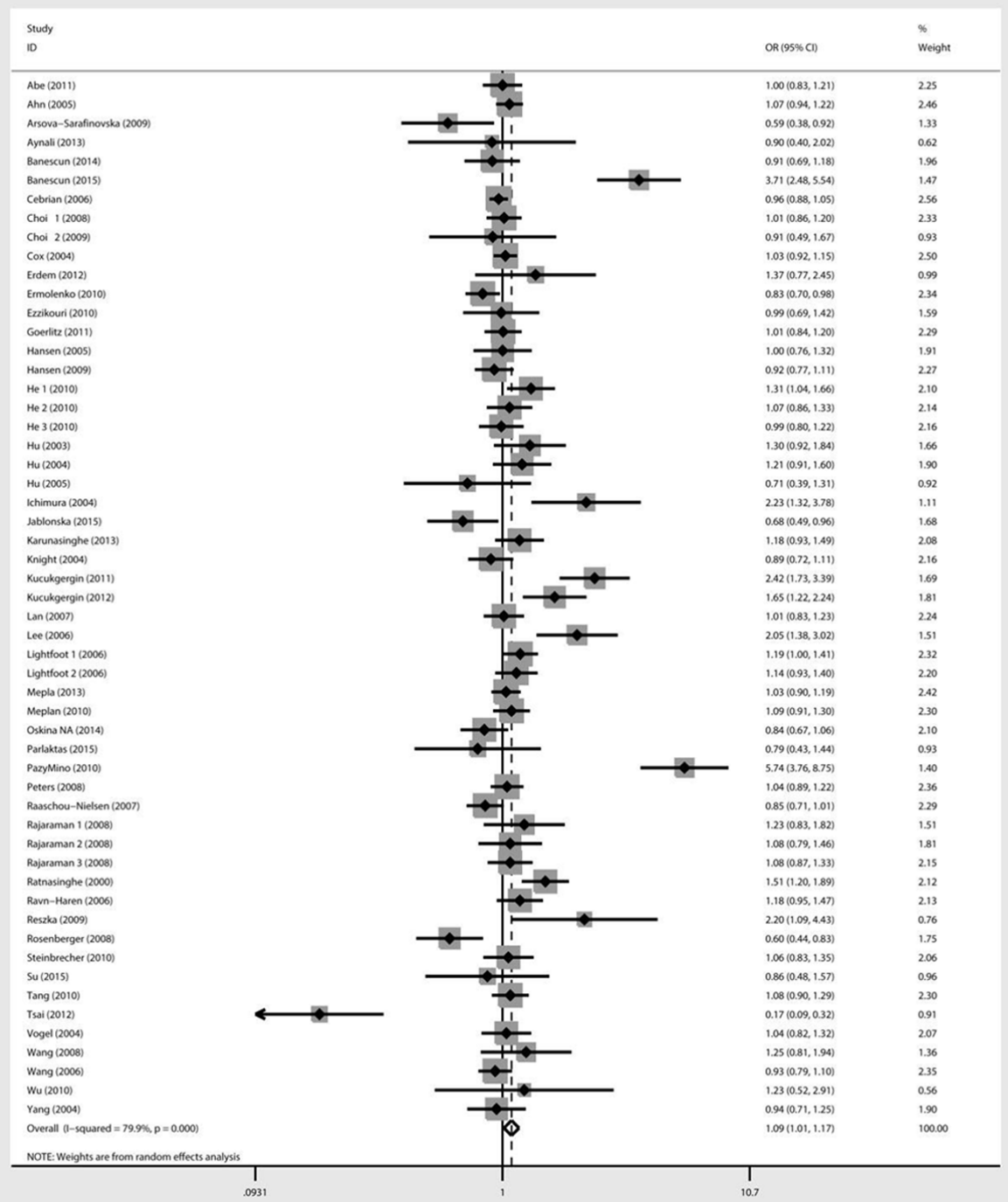

Figure 2. Forest plot for the association between the GPX1 rs1050450 polymorphism and cancer risk (T vs C). We detected significant association between the GPX1 rs1050450 polymorphism and cancer susceptibility.

= 0.71-1.61, P = 0.76), or mixed ethnicity population (OR = 1.11, 95% CI = 0.94-1.30, P = 0.216). The main results of the meta-analysis were summarized in **Table 3**.

Publication bias and sensitivity analysis

Begg's (Pr>|z| = 0.245) and Egger's (P>|t| = 0.132) test was performed to assess the publication bias of pooled literatures, which was shown in the (**Figure 3**). The shapes of the funnel plots were symmetrical in the dominant genetic models, which indicated that the publication bias did not emerge in the cohort. When dropping each study in sensitivity analysis, the results of the meta-analysis didn't change, which suggested the reliability of the results.

Table 3. The results of evidence synthesis in this meta-analysis

Variables	Dominant model (TT+CT vs CC)			Recessive model (TT vs CT+CC)			Homozygote model (TT vs CC)			Heterozygote model (CT vs CC)			Allel contrast model (T vs C)		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
All	1.08 (1.00-1.17)	0.051	70.50	1.15 (1.01-1.32)	0.042	72.00	1.15 (1.00-1.31)	0.044	66.60	1.03 (0.95-1.12)	0.42	67.80	1.09 (1.01-1.17)	0.02	79.90
By cancer type															
Prostate cancer	1.07 (0.87-1.32)	0.512	67.80	1.10 (0.81-1.48)	0.546	55.50	1.12 (0.77-1.64)	0.556	69.30	1.04 (0.84-1.29)	0.694	61.20	1.06 (0.87-1.28)	0.573	75.70
Breast cancer	0.87 (0.72-1.05)	0.132	85.60	0.98 (0.88-1.09)	0.711	0.00	0.97 (0.86-1.09)	0.57	0.00	0.87 (0.71-1.06)	0.163	86.10	0.91 (0.80-1.04)	0.148	82.40
Head and neck cancer	0.88 (0.62-1.25)	0.491	0.00	2.19 (1.39-3.46)	0.001	52.30	NA	NA	NA	0.73 (0.31-1.74)	0.482	67.90	1.17 (0.91-1.51)	0.215	0.00
Hematological malignancies	1.13 (0.94-1.37)	0.203	55.70	1.29 (0.73-2.30)	0.383	91.00	1.20 (0.82-1.76)	0.341	69.10	1.11 (0.99-1.25)	0.082	37.00	1.22 (0.95-1.57)	0.125	88.30
Brain cancer	1.19 (1.03-1.37)	0.018	0.00	0.98 (0.69-1.39)	0.886	0.00	1.07 (0.74-1.54)	0.735	0.00	1.22 (0.98-1.52)	0.082	0.00	1.1 (0.94-1.29)	0.244	0.00
Digestive system cancer	1.02 (0.93-1.13)	0.65	7.90	1.07 (0.89-1.29)	0.464	0.00	1.06 (0.87-1.29)	0.559	0.00	1.01 (0.91-1.12)	0.803	35.10	1.03 (0.95-1.11)	0.507	0.00
Bladder cancer	1.72 (1.09-2.70)	0.019	82.70	3.56 (1.42-8.94)	0.007	87.40	3.75 (1.41-9.94)	0.008	87.80	1.24 (0.89-1.74)	0.203	62.10	1.94 (1.17-3.22)	0.01	91.90
Skin cancer	1.11 (0.96-1.28)	0.175	0.00	1.15 (0.89-1.49)	0.293	49.10	1.19 (0.91-1.56)	0.202	48.20	1.09 (0.94-1.27)	0.275	0.00	1.09 (0.97-1.22)	0.132	14.70
Lung cancer	1.17 (0.79-1.75)	0.431	87.00	0.82 (0.49-1.37)	0.445	73.90	0.82 (0.41-1.66)	0.588	84.70	1.19 (0.77-1.86)	0.433	86.80	1.07 (0.74-1.55)	0.709	89.60
By ethnicity															
Caucasian	1.06 (0.98-1.15)	0.132	63.80	1.08 (0.94-1.25)	0.276	68.20	1.08 (0.94-1.24)	0.304	62.30	1.04 (0.96-1.12)	0.362	57.60	1.06 (0.98-1.14)	0.139	75.60
Mixed	1.11 (0.94-1.30)	0.216	64.30	1.44 (0.98-2.11)	0.067	82.00	1.41 (0.98-2.04)	0.065	78.20	0.99 (0.85-1.16)	0.943	53.80	1.19 (0.98-1.45)	0.077	85.20
AfricanAmerican	1.07 (0.71-1.61)	0.76	0.00	1.24 (0.32-4.76)	0.751	65.10	1.56 (0.88-2.77)	0.133	48.00	0.91 (0.58-1.43)	0.679	0.00	1.19 (0.88-1.61)	0.258	0.00
Asian	1.04 (0.47-2.30)	0.915	91.60	NA	NA	NA	NA	NA	NA	1.05 (0.47-2.32)	0.912	91.60	1.02 (0.50-2.07)	0.954	90.50
By HWE															
Yes	1.07 (1.00-1.15)	0.041	62.20	1.11 (0.99-1.25)	0.081	61.60	1.13 (0.99-1.29)	0.059	64.30	1.04 (0.97-1.11)	0.336	56.60	1.08 (1.01-1.15)	0.025	73.10
No	0.82 (0.17-4.09)	0.809	94.40	2.08 (0.22-19.66)	0.523	97.00	2.55 (0.17-37.87)	0.496	93.50	0.64 (0.14-3.01)	0.575	93.70	0.86 (0.21-3.54)	0.836	97.20

P, *P*-value of Z-test to evaluate the significance of the ORs; NA, not available.

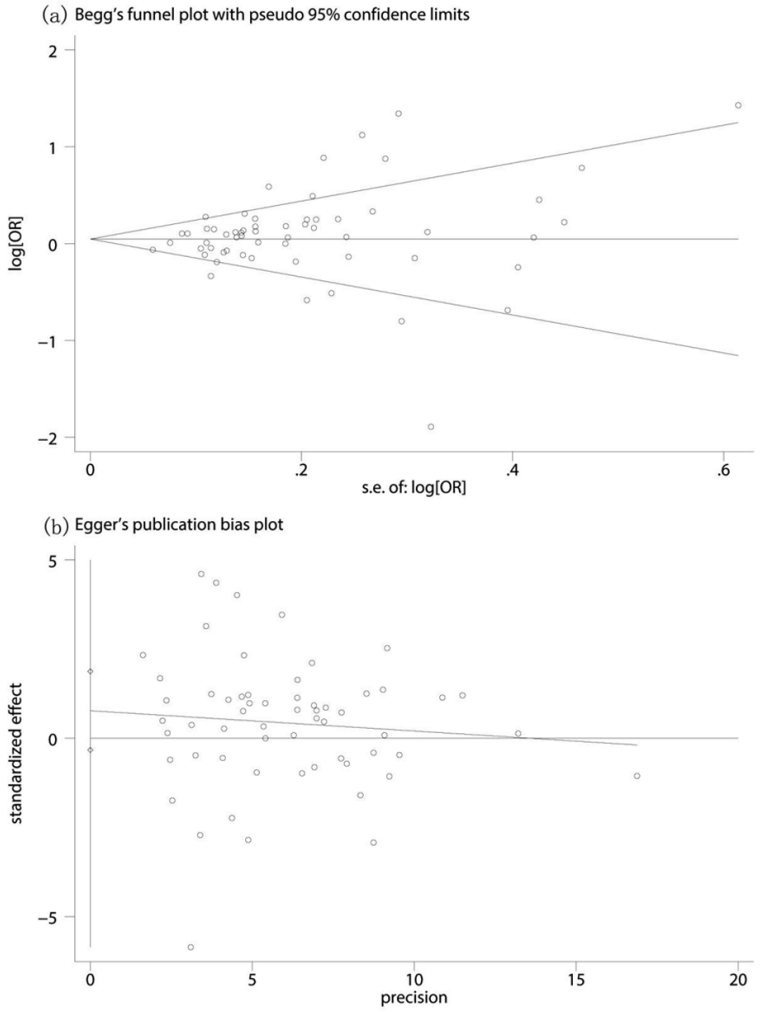

Figure 3. Begg's funnel plot and Egger's on publication bias for included studies on the association of the GPX1 rs1050450 polymorphism and cancer susceptibility (TT vs CT+CC). The funnel plot seemed symmetrical, suggesting absence of publication bias.

Discussion

The current meta-analysis, including 21,296 cancer patients and 30,346 controls from 60 case-control studies, investigated the relationship between the GPX1 (rs1050450) polymorphism and cancer risk. To the best of our knowledge, this was the first meta-analysis in such a large sample size with comprehensive evaluation of the association between the polymorphism of GPX1 and the tumor risk. We found that individuals with TT/CT genotypes harbored increased risk of cancer, especially in patients with bladder cancer as shown in the subgroup analysis.

Oxidative stress is an inevitable result of aerobic life. Previous studies have suggested that reactive oxygen species (ROS)-related oxidative damage plays a vital role in carcinogenesis [1]. ROS are modulated by regular metabolic process in vivo and can initiate a series of free radical formation. ROS can result in the breakage of DNA, oxidization of proteins and lipid [2]. DNA damages may inactivate cancer suppressor genes and further reduce the integrity of genome [37]. GPX1 plays a crucial role in the detoxification of mitochondrial ROS. High level expression of GPX1 could increase the antioxidant capacity in one cell, thus reducing intracellular oxidative stress. The appropriate adjustment of GPX1 levels has been considered as a significant factor in different stages of carcinogenesis both in vitro and vivo experiments [60]. Accumulating evidences have demonstrated that the GPX1 (rs1050450 C>T) polymorphism may increase carcinogenesis risk. According to our study, the result indicated that individuals with the CT/TT (Pro-Leu/LeuLeu) genotypes were associated with a higher risk of cancer than subjects carrying the wild ProPro genotype.

Since cancer origins could influence the outcomes as shown in previous studies, we conducted subgroup analysis according to cancer types. Except for bladder cancer and brain tumor, we did not find any positive association regarding to prostate cancer, breast cancer, lung cancer, colorectal cancer, NHL, skin cancer, digestive system cancer and head and neck cancer. Prostate cancer and bladder cancer are two of the most common urological malignancies. Previous studies suggested that the association of GPX1 (rs1050450) polymorphism with prostate cancer and bladder cancer was inconclusive [22, 27, 34, 37]. Therefore, current meta-analysis was designed to determine a more accurate role of GPX (rs1050450 C>T) polymorphism since this meta-analysis

investigated a large number of individuals and could also estimate the effect of genetic factors [8]. In addition, we previously put forward that only two studies reported African-Americans and only five studies reported Asian population. Hence, larger-sample studies and combined analysis are warranted to further verify the role of ethnic discrepancy in the relationship of the GPX1 polymorphism and cancer risks, especially for African-Americans and Asians.

In interpreting current results, several limitations of the meta-analysis should be addressed. First, as only publications indexed by selected databases were included in the current study, some relevant published studies with null results were missing and ongoing studies with unpublished data were unavailable, which may have influenced our results. Second, part of the studies investigated comparing several different sets of cases with the same set of control, which might reduce the statistical power for identifying those possible associations. Third, the lack of the original data of the reviewed studies limited our further evaluation of the potential interactions. In the meantime, current study also had some merits. For one thing, over 60 studies were pooled from 52 publications, which significantly increased statistical power of the analysis. For another, on the basis of our studies, we found a novel way to predict the association between GPX (rs1050450 C>T) polymorphism and cancer risk, especially in bladder cancer.

To summarize, the results from the meta-analysis provided some evidence that the GPX1 Pro198Leu (rs1050450 C>T) polymorphism might contribute to genetic susceptibility to cancer especially in bladder cancer, supporting the hypothesis that the polymorphism could serve as a potential tumor predicting biomarker. However, the conclusion should be interpreted with caution. The detailed analysis of genetic models and inclusion of large-scale studies regarding African-Americans and Asians, and comprehensive study design with respect to gene-gene and gene-environment interaction are warranted.

Acknowledgements

This work was funded by the National Natural Science Foundation of China (Grant No. 81171320).

Disclosure of conflict of interest

None.

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