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Original Article

Peroxisome proliferator-activated receptor gamma (*PPARG*) rs1801282 C>G polymorphism is associated with cancer susceptibility in asians: an updated meta-analysis

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Abstract: *Peroxisome proliferator-activated receptor gamma* (*PPARG*) is related to inflammation and plays an important role in the development of cancer. *PPARG* rs1801282 C>G polymorphism might influence the risk of cancer by regulating production of *PPARG* gene. Hence, a comprehensive meta-analysis was conducted to explore the association of *PPARG* rs1801282 C>G polymorphism with cancer susceptibility. An extensive search of PubMed and Embase databases for all relevant publications was carried out. A total of 38 publications with 16,844 cancer cases and 23,736 controls for *PPARG* rs1801282 C>G polymorphism were recruited in our study. Our results indicated that *PPARG* rs1801282 C>G variants were associated with an increased cancer risk in Asian populations and gastric cancer. In summary, the findings suggest that PPARG rs1801282 C>G polymorphism may play a crucial role in malignant transformation and the development of cancer.

Keywords: Cancer, polymorphism, *peroxisome proliferator-activated receptor gamma*, meta-analysis

Introduction

With the dramatic increase of the incidence of cancer and cancer-relative mortality, cancer has become one of the major public health burdens. For this reason, novel cancer biomarkers are needed urgently for prevention and early detection of malignance. Carcinogenesis is a very complicated process and has not been fully understood. It is believed that the development of cancer is influenced by susceptibility genes and environmental factors.

Peroxisome proliferator-activated receptor gamma (PPARG), a type of nuclear hormone receptor, acts as an important transcriptional regulator of cellular differentiation, carbohydrate and lipid metabolism [1]. PPARG also owns certain anti-inflammatory properties [2, 3]. Activation of PPARG reduces the production of multiple cytokines (e.g., interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha) by antagonizing the role of the signal transducer and activator of transcription, nuclear factor kappa-B and transcription factors activator protein 1, which suppresses induction of the inflammatory response [4, 5]. Since PPARG has been supported to take part in cell growth and differentiation, it has been hypothesized that the disorder of PPARG contributes to malignant transformation and the development of cancer. The *PPARG* rs1801282 C>G polymorphism, a SNP in exon 2 of *PPARG*, encodes a proline→alanine substitution at amino acid residue 12 (Pro12Ala). This mutation reduces the transcription of *PPARγ2* [3]. The *PPARG* rs1801282

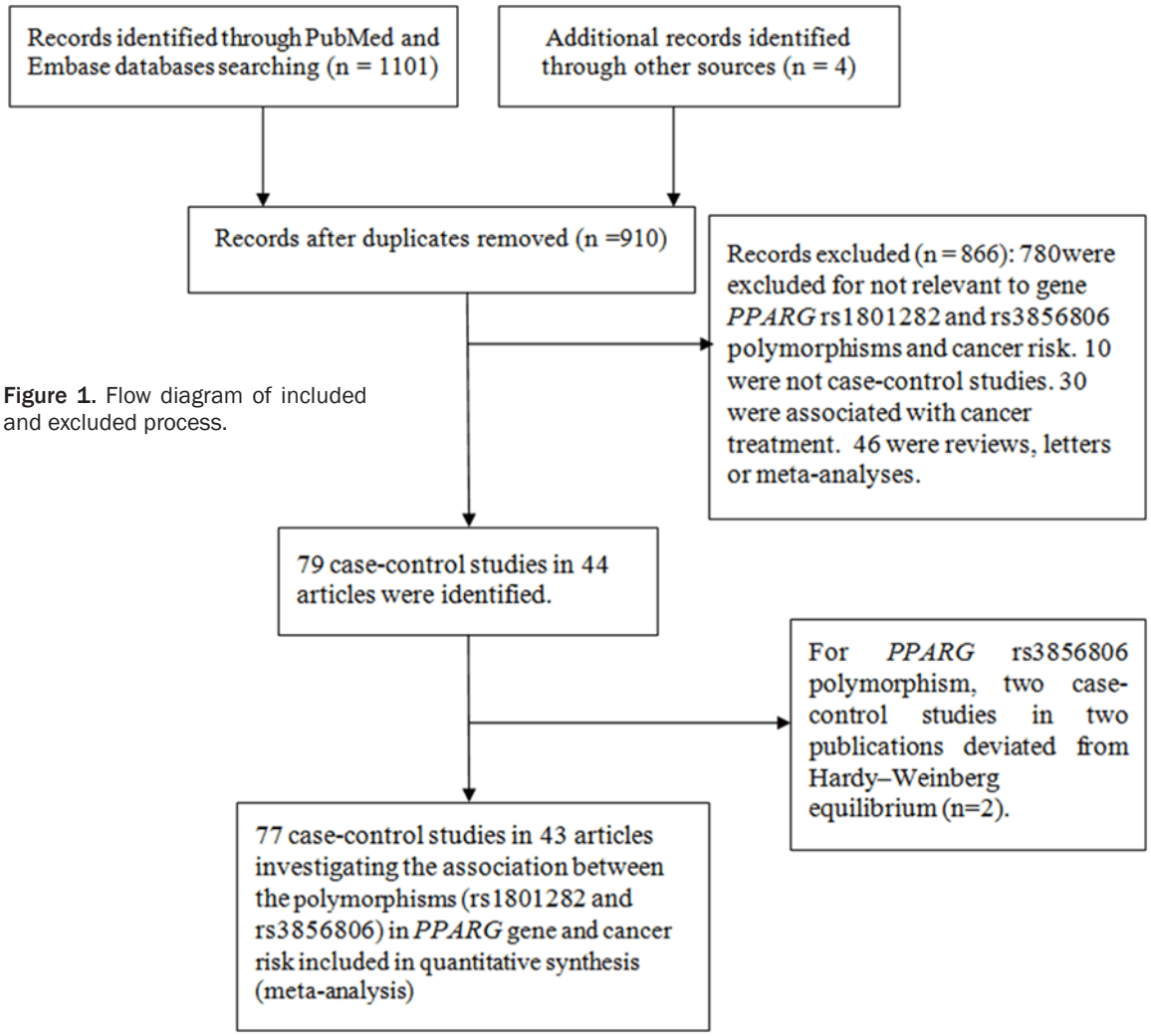

Figure 1. Flow diagram of included and excluded process.

C>G polymorphism has been extensively investigated and was found to be correlated with the risk of cardiovascular diseases and type 2 diabetes [6-9]. Furthermore, the evidence is mounting that *PPARG* rs1801282 C>G polymorphism might affect individual susceptibility to certain types of malignancy (e.g., gastric cancer, pancreatic cancer, breast cancer and colorectal cancer) [10-14].

Recently, the association between this polymorphism in *PPARG* gene and cancer risk was extensively examined. A meta-analysis supported that *PPARG* rs1801282 C>G polymorphism was associated with the increased risk of gastric cancer, but this polymorphism was not correlated with overall cancer risk [15]. Up to now, 43 publications focus on the correlation of the *PPARG* rs1801282 C>G polymorphism with cancer risk, and the observed results remain conflicting. In the present study, we harnessed an updated meta-analysis on the eligible studies to further investigate the association of *PPARG* rs1801282 C>G polymorphism with the risk of cancer.

Materials and methods

Search strategy

Eligible publications were extracted by exhaustively electronic search of PubMed and Embase databases using the following terms: (Peroxisome proliferator activated receptor gamma or PPARγ or PPARG) and (polymorphism or SNP or mutation or variant) and (cancer or carcinoma or malignance). References of retrieved studies, comments, meta-analyses, reviews and letters were manually searched for additional publications. There was no limitation of

Table 1. Characteristics of all included studies in the meta-analysis

study	Publication year	Ethnicity	Country	Cancer type	Sample size (case/control)	Genotype method
Kopp et al.	2013	Caucasians	Denmark	prostate cancer	370/370	RT-PCR
Martinez-Nava et al.	2013	mixed	Mexico	breast cancer	208/220	RT-PCR
Canbay et al.	2012	Caucasians	Turkey	gastric cancer	86/129	PCR-RFLP
Crous-Bou et al.	2012	Caucasians	Israel	colorectal cancer	1780/1864	Illumina Beadstation and BeadExpress
Petersen et al.	2012	Caucasians	Denmark	breast cancer	798/798	TaqMan
Abuli et al.	2011	Caucasians	Spain	colorectal cancer	515/502	MALDI-TOF MS
Tang et al.	2011	mixed	USA	pancreatic cancer	1070/1175	TaqMan
Lim et al.	2011	Asians	Singapore	lung cancer	298/718	RT-PCR
Wu et al.	2011	Asians	China	breast cancer	291/589	RT-PCR
Bazargani et al.	2010	Caucasians	Iran	gastric cancer	79/152	PCR–RFLP
Pinheiro et al.	2010	Caucasians	UK	ovarian cancer	233/663	Taqman
Pinheiro et al.	2010	Caucasians	UK	ovarian cancer	1120/1160	Taqman
Tsilidis et al.	2009	mixed	USA	colorectal cancer	208/381	Taqman
Fesinmeyer et al.	2009	mixed	USA	pancreatic cancer	83/166	TaqMan
Wang et al.	2009	mixed	USA	prostate cancer	258/258	TaqMan
Kury et al.	2008	Caucasians	France	colorectal cancer	1023/1121	TaqMan
Prasad et al.	2008	Asians	India	gastric cancer	62/286	PCR-RFLP
Tahara et al.	2008	Asians	Japan	gastric cancer	215/201	PCR-RFLP
Vogel et al.	2008	Caucasians	Denmark	lung cancer	403/744	TaqMan
Justenhoven et al.	2008	Caucasians	German	breast cancer	688/724	MALDI-TOF MS
Gallicchio et al.	2007	Caucasians	USA	breast cancer	61/933	TaqMan
Wang et al.	2007	Caucasians	USA	breast cancer	488/488	TaqMan
Mossner et al.	2007	Caucasians	German	melanoma	335/355	PCR-RFLP
Mossner et al.	2007	Caucasians	German	melanoma	497/435	PCR-RFLP
Vogel et al.	2007	Caucasians	Denmark	colorectal cancer	355/753	TaqMan
Zhang et al.	2007	Asians	China	lung cancer	45/45	DNA sequence
Vogel et al.	2007	Caucasians	Denmark	skin cancer	304/315	TaqMan
Kuriki et al.	2006	Asians	Japan	colorectal cancer	128/238	PCR-CTPP, PCR-RFLP
Theodoropoulos et al.	2006	Caucasians	Greece	colorectal cancer	222/200	PCR-RFLP
Liao et al.	2006	Asians	China	gastric cancer	104/104	PCR-RFLP
Siezen et al.	2006	Caucasians	The netherlands	colorectal cancer	204/399	DNA sequence
Siezen et al.	2006	Caucasians	The netherlands	colorectal cancer	487/750	DNA sequence
Slattery et al.	2005	mixed	USA	colorectal cancer	2371/2972	TaqMan
McGreavey et al.	2005	Caucasians	UK	colorectal cancer	478/733	TaqMan
Jiang et al.	2005	Asians	India	colorectal cancer	59/291	PCR-RFLP
Jiang et al.	2005	Asians	India	colorectal cancer	242/291	PCR-RFLP
Campa et al.	2004	Caucasians	Norway	lung cancer	250/214	TaqMan
Landi et al.	2003	Caucasians	Spain	colorectal cancer	139/326	TaqMan
Landi et al.	2003	Caucasians	Spain	colorectal cancer	238/326	TaqMan
Paltoo et al.	2003	Caucasians	Finland	prostate cancer	193/188	MALDI-TOF
Memisoglu et al.	2002	mixed	USA	breast cancer	725/953	PCR-RFLP
Smith et al.	2001	Caucasians	UK	Renal cell carcinoma	40/62	DGGE
Smith et al.	2001	Caucasians	UK	ovarian cancer	31/62	DGGE
Smith et al.	2001	Asians	Japan	ovarian cancer	28/215	DGGE
Smith et al.	2001	Asians	Japan	cervical cancer	20/215	DGGE
Smith et al.	2001	Asians	Japan	bladder cancer	31/215	DGGE
Smith et al.	2001	mixed	USA	ovarian cancer	26/80	DGGE
Smith et al.	2001	mixed	USA	endometrial cancer	69/80	DGGE
Smith et al.	2001	mixed	USA	prostate cancer	38/80	DGGE
Zhou et al.	2000	mixed	USA	glioblastoma	52/80	PCR
Zhou et al.	2000	Caucasians	German	glioblastoma	44/60	PCR

RT-PCR: reverse transcription-polymerase chain reaction. MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. PCR-CTPP: polymerase chain reaction with confronting two-pair primers. DGGE: denaturing gradient gel electrophoresis.

Table 2. Distribution of *PPARG* rs1801282 C>G polymorphism genotype and allele among cases and controls

Study	Publication year	Case			Control			Case		Control		HWE
		CC	CG	GG	CC	CG	GG	G	C	G	C	
Kopp et al.	2013	241	90	3	245	87	2	96	572	91	577	0.050905
Martı´nez-Nava et al.	2013	165	43	0	169	49	2	43	373	53	387	0.448105
Canbay et al.	2012	68	14	4	116	12	1	22	150	14	244	0.287345
Crous-Bou et al.	2012	710	102	0	1307	163	9	102	1522	181	2777	0.117069
Petersen et al.	2012	616	167	15	569	209	20	197	1399	249	1347	0.87691
Abuli et al.	2011	426	87	2	419	80	3	91	939	86	918	0.697001
Tang et al.	2011	826	216	10	871	236	23	236	1868	282	1978	0.140851
Lim et al.	2011	274	23	1	653	64	1	25	571	66	1370	0.660099
Wu et al.	2011	260	29	0	546	40	0	29	549	40	1132	0.392337
Bazargani et al.	2010	60	18	1	134	17	1	20	138	19	285	0.573866
Pinheiro et al.	2010	166	56	2	487	144	13	60	388	170	1118	0.540142
Pinheiro et al.	2010	831	228	16	882	241	13	260	1890	267	2005	0.441786
Tsilidis et al.	2009	165	37	1	295	68	6	39	367	80	658	0.370123
Fesinmeyer et al.	2009	60	22	1	139	27	0	24	142	27	305	0.254053
Wang et al.	2009	198	57	0	189	58	7	57	453	72	436	0.327667
Kury et al.	2008	822	194	7	896	212	13	208	1838	238	2004	0.9079
Prasad et al.	2008	39	18	5	214	67	5	28	96	77	495	0.926116
Tahara et al.	2008	194	21	0	193	8	0	21	409	8	394	0.773449
Vogel et al.	2008	301	93	9	544	187	13	111	695	213	1275	0.502205
Justenhoven et al.	2008	452	135	6	462	145	15	147	1039	175	1069	0.372101
Gallicchio et al.	2007	48	7	1	689	188	18	9	103	224	1566	0.223793
Wang et al.	2007	376	87	15	375	98	5	117	839	108	848	0.615475
Mossner et al.	2007	239	84	11	258	86	7	106	562	100	602	0.957311
Mossner et al.	2007	372	115	7	324	102	6	129	859	114	750	0.522918
Vogel et al.	2007	252	96	7	550	190	13	110	600	216	1290	0.460144
Zhang et al.	2007	39	6	0	41	4	0	6	84	4	86	0.755033
Vogel et al.	2007	220	83	1	232	77	6	85	523	89	541	0.894139
Kuriki et al.	2006	120	7	0	221	17	0	7	247	17	459	0.567742
Theodoropoulos et al.	2006	164	48	10	118	70	12	68	376	94	306	0.707193
Liao et al.	2006	84	17	3	95	9	0	23	185	9	199	0.644642
Siezen et al.	2006	160	40	1	325	70	2	42	360	74	720	0.389723
Siezen et al.	2006	387	92	8	596	146	8	108	866	162	1338	0.723797
Slattery et al.	2005	1840	496	35	2283	645	44	566	4176	733	5211	0.839204
McGreavey et al.	2005	366	80	9	403	100	10	98	812	120	906	0.202319
Jiang et al.	2005	46	13	0	230	57	4	13	105	65	517	0.768946
Jiang et al.	2005	194	44	4	230	57	4	52	432	65	517	0.768946
Campa et al.	2004	2	52	192	4	47	161	436	56	369	55	0.792322
Landi et al.	2003	111	15	3	243	61	5	21	237	71	547	0.60618
Landi et al.	2003	200	31	0	243	61	5	31	431	71	547	0.60618
Paltoo et al.	2003	121	64	8	128	54	6	80	306	66	310	0.916738
Memisoglu et al.	2002	563	148	14	752	190	11	176	1274	212	1694	0.795703
Smith et al.	2001	37	3	0	49	11	2	3	77	15	109	0.191855
Smith et al.	2001	27	4	0	49	11	2	4	58	15	109	0.191855
Smith et al.	2001	27	1	0	203	11	1	1	55	13	417	0.061618
Smith et al.	2001	19	1	0	203	11	1	1	39	13	417	0.061618

Smith et al.	2001	29	2	0	203	11	1	2	60	13	417	0.061618
Smith et al.	2001	21	5	0	68	12	0	5	47	12	148	0.468322
Smith et al.	2001	56	13	0	68	12	0	13	125	12	148	0.468322
Smith et al.	2001	34	4	0	68	12	0	4	72	12	148	0.468322
Zhou et al.	2000	37	15	0	68	12	0	15	89	12	148	0.468322
Zhou et al.	2000	35	9	0	46	14	0	9	79	14	106	0.306283

HWE: Hardy-Weinberg equilibrium.

Table 3. Different comparative genetic models results of this meta-analysis in the subgroup analysis by race

Polymorphism	Genetic comparison	Population	OR (95% CI); *P*	Test of heterogeneity	
				(*p*-Value, I^2)	Model
rs1801282 C>G	GG+CG vs. CC	All	1.00 (0.93-1.07); 0.987	0.007, 35.7%	R
		Asians	1.23 (1.01-1.50); 0.039	0.272, 17.6%	F
		Caucasians	0.96 (0.88-1.05); 0.402	0.009, 43.2%	R
		Mixed	0.98 (0.90-1.07); 0.656	0.305, 14.6%	F
	GG vs. CG+CC	All	0.97 (0.83-1.14); 0.713	0.175, 16.8%	F
		Asians	2.36 (1.15-4.86); 0.020	0.808, 0.0%	F
		Caucasians	0.98 (0.80-1.18); 0.800	0.415, 3.3%	F
		Mixed	0.76 (0.39-1.45); 0.399	0.055, 51.4%	R
	GG vs. CC	All	0.94 (0.79-1.12); 0.511	0.101, 22.5%	F
		Asians	2.43 (1.18-5.01); 0.016	0.785, 0.0%	F
		Caucasians	0.94 (0.75-1.16); 0.543	0.302, 11.0%	F
		Mixed	0.75 (0.39-1.46); 0.399	0.049, 52.6%	R
	CG vs. CC	All	1.00 (0.93-1.07); 0.956	0.047, 26.3%	R
		Asians	1.20 (0.98-1.47); 0.083	0.439, 0.5%	F
		Caucasians	0.96 (0.88-1.05); 0.402	0.023, 37.9%	R
		Mixed	0.99 (0.91-1.09); 0.870	0.488, 0.0%	F
	G vs. C	All	1.00 (0.94-1.07); 0.952	0.001, 42.3%	R
		Asians	1.25 (1.04-1.51); 0.018	0.145, 30.8%	F
		Caucasians	0.97 (0.89-1.05); 0.466	0.005, 45.6%	R
		Mixed	0.97 (0.89-1.05); 0.459	0.158, 30.3%	F

F indicates fixed model; R indicates random model.

language and the last research was performed on July 15, 2014.

Inclusion and exclusion criteria

Inclusion criteria were defined as follows: (a) The publications assessed the association of *PPARG* rs1801282 C>G polymorphism with cancer risk; (b) The studies designed as a case-control or cohort study; (c) The sufficient data could be extracted to calculate an odds ratio (OR) with its 95% CI; (d) In these articles, the genotype distributions among controls were consistent with Hardy-Weinberg equilibrium (HWE). The major exclusion criteria were: (a) not a case-control or cohort study; (b) overlapping data; (c) comments, letters, reviews, animal studies and editorials; (d) cancer prognosis and treatment. In certain publications, the data were reported on different subgroups; we treated them as separate studies.

Data extraction

From each eligible study, data were extracted independently by three authors (Y. Wang, Y. Chen and H. Jiang). The following terms were collected: the surname of first author, year of publication, country, numbers of subjects and genotype frequencies of cases and controls, cancer type, ethnicity, genotyping method, and evidence of HWE in controls. If there were any

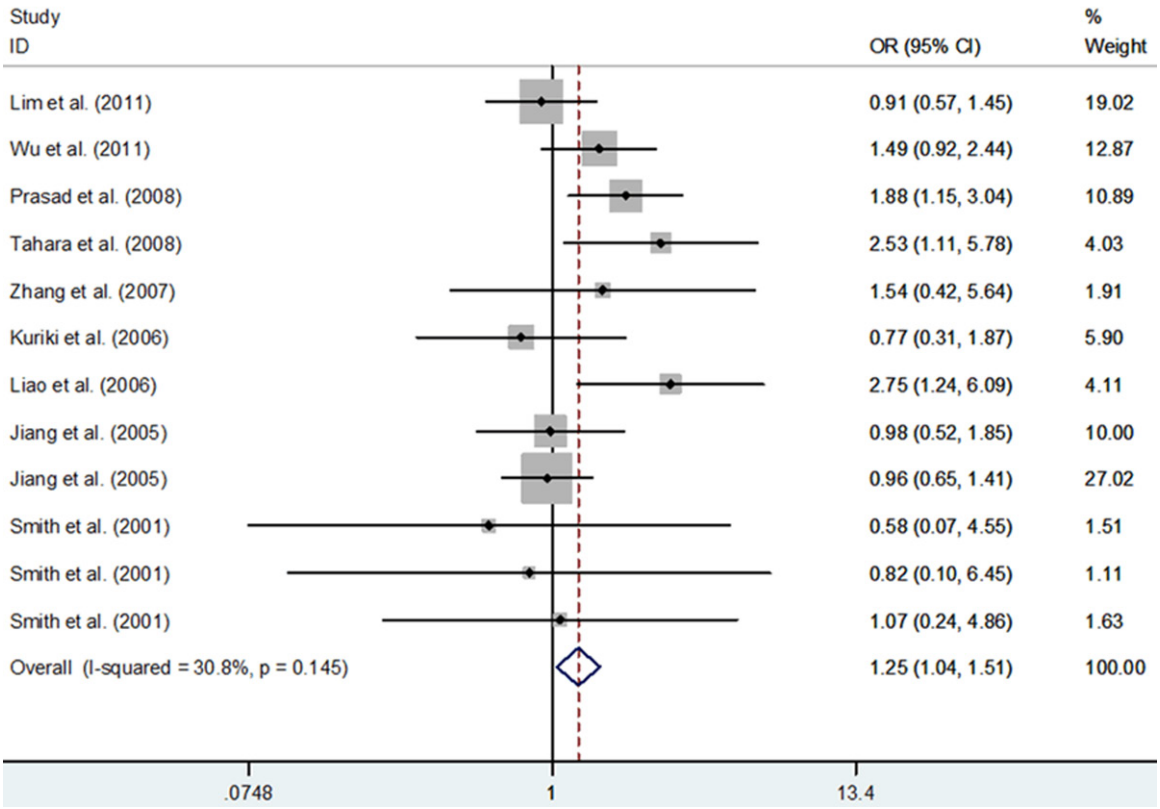

Figure 2. Meta-analysis with a fixed-effect for the association of cancer risk with the *PPARG* rs1801282 C>G polymorphism in Asians (allele comparing model).

discrepancies, they were resolved following a discussion between all reviewers.

Statistical analysis

HWE in controls was tested by a web-based Pearson's χ^2 test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). We used crude ORs with corresponding 95% CIs as an assessment of the association between *PPARG* rs1801282 C>G polymorphism with cancer risk. A $P<0.05$ was considered significant. Heterogeneities were assessed using Cochran's Q-statistic and I^2 test. When $I^2>50\%$ or $P<0.10$, there was significant heterogeneity, then the random-effects model was applied [16], otherwise, the fixed-effects model was used [17]. Subgroup analyses were conducted by ethnicity and cancer type. Sensitivity analysis was performed by nonparametric "trim-and-fill" method. The Begg's test and Egger's test were both used to determine the evidence of publication bias [18]. For publication bias test, statistical significance was defined as $P<0.1$. In our study, all the statistical analyses were conducted with Stata 12.0 software (StataCorp LP, College Station, TX) and *P* values were two-sided.

Results

Characteristics of studies

As shown in **Figure 1**, a total of 1101 publications were retrieved. According to the inclusion criteria and exclusion criteria, there were 38 publications (including 51 individual studies) on the *PPARG* rs1801282 C>G polymorphism [10, 11, 13, 14, 19-52]. Among them, fifteen investigated colorectal cancer [13, 14, 19-28], seven investigated breast cancer [12, 29-33, 35], five investigated ovarian cancer [36, 37], five investigated gastric cancer [10, 38-41], four investigated lung cancer [42-45], four investigated prostate cancer [37, 46-48], two investigated pancreatic cancer [11, 49], two investigated melanoma [50] and two investigated glioblastoma [51]. Other articles investigated skin cancer [52], endometrial cancer [37], bladder cancer [37], cervical cancer [37] and renal cell carcinoma [37]. Among these, 28 were from

Table 4. Different comparative genetic models results of this meta-analysis in the subgroup analysis by cancer type

Polymorphism	Genetic comparison	Cancer type	OR (95% CI); *P*	Test of heterogeneity	
				(*p*-Value, I^2)	Model
rs1801282 C>G	GG+CG vs. CC	All	1.00 (0.93-1.07); 0.987	0.007, 35.7%	R
		Prostate cancer	1.02 (0.82-1.27); 0.836	0.482, 0.0%	F
		Breast cancer	0.93 (0.78-1.10); 0.395	0.076, 47.5%	R
		Gastric cancer	2.22 (1.61-3.07); <0.001	0.922, 0.0%	F
		Colorectal cancer	0.94 (0.87-1.02); 0.131	0.125, 30.6%	F
		Pancreatic cancer	1.27 (0.61-2.65); 0.529	0.024, 80.2%	R
		Lung cancer	0.95 (0.75-1.19); 0.636	0.623, 0.0%	F
		Ovarian cancer	1.02 (0.86-1.21); 0.792	0.828, 0.0%	F
		Melanoma	1.03 (0.83-1.29); 0.764	0.619, 0.0%	F
		Glioblastoma	1.42 (0.53-3.79); 0.481	0.125, 57.6%	R
		Other cancers	1.01 (0.74-1.37); 0.968	0.459, 0.0%	F
	GG vs. CG+CC	All	0.97 (0.83-1.14); 0.713	0.175, 16.8%	F
		Prostate cancer	0.76 (0.16-3.58); 0.726	0.104, 55.8%	R
		Breast cancer	1.00 (0.51-1.98); 0.991	0.045, 55.9%	R
		Gastric cancer	4.95 (1.86-13.16); 0.001	0.910, 0.0%	F
		Colorectal cancer	0.86 (0.65-1.12); 0.258	0.770, 0.0%	F
		Pancreatic cancer	1.02 (0.10-10.55); 0.985	0.126, 57.4%	R
		Lung cancer	1.17 (0.80-1.72); 0.420	0.845, 0.0%	F
		Ovarian cancer	0.98 (0.53-1.80); 0.946	0.497, 0.0%	F
		Melanoma	1.35 (0.66-2.78); 0.409	0.506, 0.0%	F
		Glioblastoma	NA	NA	NA
		Other cancers	0.40 (0.10-1.51); 0.174	0.319, 14.5%	F
	GG vs. CC	All	0.94 (0.79-1.12); 0.511	0.101, 22.5%	F
		Prostate cancer	0.77 (0.16-3.81); 0.752	0.094, 57.7%	R
		Breast cancer	0.97 (0.49-1.93); 0.930	0.039, 57.2%	R
		Gastric cancer	5.51 (2.06-14.79); 0.001	0.920, 0.0%	F
		Colorectal cancer	0.83 (0.63-1.09); 0.183	0.729, 0.0%	F
		Pancreatic cancer	1.12 (0.09-13.61); 0.931	0.107, 61.6%	R
		Lung cancer	1.49 (0.72-3.09); 0.287	0.756, 0.0%	F
		Ovarian cancer	0.98 (0.54-1.81); 0.960	0.507, 0.0%	F
		Melanoma	1.36 (0.66-2.80); 0.402	0.492, 0.0%	F
		Glioblastoma	NA	NA	NA
		Other cancers	0.39 (0.10-1.50); 0.172	0.319, 14.6%	F
	CG vs. CC	All	1.00 (0.93-1.07); 0.956	0.047, 26.3%	R
		Prostate cancer	1.05 (0.84-1.31); 0.684	0.693, 0.0%	F
		Breast cancer	0.91 (0.80-1.02); 0.108	0.118, 40.9%	F
		Gastric cancer	2.01 (1.44-2.82); <0.001	0.820, 0.0%	F
		Colorectal cancer	0.95 (0.88-1.03); 0.207	0.113, 32.0%	F
		Pancreatic cancer	1.26 (0.66-2.39); 0.485	0.050, 73.9%	R
		Lung cancer	0.92 (0.73-1.17); 0.507	0.637, 0.0%	F
		Ovarian cancer	1.03 (0.87-1.22); 0.747	0.872, 0.0%	F
		Melanoma	1.01 (0.80-1.27); 0.914	0.763, 0.0%	F
		Glioblastoma	1.42 (0.53-3.79); 0.481	0.125, 57.6%	R
		Other cancers	1.08 (0.79-1.47); 0.642	0.578, 0.0%	F
	G vs. C	All	1.00 (0.94-1.07); 0.952	0.001, 42.3%	R

Prostate cancer	1.00 (0.82-1.21); 0.981	0.278, 22.1%	F
Breast cancer	0.94 (0.80-1.12); 0.515	0.040, 54.5%	R
Gastric cancer	2.26 (1.69-3.02); <0.001	0.909, 0.0%	F
Colorectal cancer	0.94 (0.88-1.01); 0.091	0.195, 23.4%	F
Pancreatic cancer	1.23 (0.59-2.60); 0.580	0.014, 83.4%	R
Lung cancer	1.00 (0.83-1.21); 0.993	0.743, 0.0%	F
Ovarian cancer	1.01 (0.87-1.18); 0.857	0.739, 0.0%	F
Melanoma	1.05 (0.86-1.29); 0.616	0.497, 0.0%	F
Glioblastoma	1.37 (0.58-3.23); 0.477	0.150, 51.8%	R
Other cancers	0.94 (0.71-1.24); 0.652	0.392, 2.5%	F

F indicates fixed model; R indicates random model.

Caucasians, 12 were from Asians and 11 were from mixed populations. The characteristics are summarized in **Table 1**. The genotype distributions are listed in **Table 2**.

Quantitative synthesis

In total, 51 studies with 16,844 cancer cases and 23,736 controls focused on the relationship of *PPARG* rs1801282 C>G polymorphism with cancer risk. Overall, our results did not support any statistical evidence of the association between *PPARG* rs1801282 C>G polymorphism and cancer. As Caucasians, Asians and mixed populations were involved in our study, we performed subgroup analyses base on different ethnicities. The results showed that *PPARG* rs1801282 C>G polymorphism was a risk factor for cancer in Asians: GG+CG vs. CC (OR, 1.23; 95% CI, 1.01-1.50; *P* = 0.039), GG vs. CG+CC (OR, 2.36; 95% CI, 1.15-4.86; *P* = 0.020), GG vs. CC (OR, 2.43; 95% CI, 1.18-5.01; *P* = 0.016) and G vs. C (OR, 1.25; 95% CI, 1.04-1.51; *P* = 0.018) (**Table 3**; **Figure 2**). With respect to a subgroup analysis by cancer type, the results of the combined analyses showed that *PPARG* rs1801282 C>G polymorphism was associated with gastric cancer risk in five genetic models: GG+CG vs. CC (OR, 2.22; 95% CI, 1.61-3.07; *P*<0.001), GG vs. CG+CC (OR, 4.95; 95% CI, 1.86-13.16; *P* = 0.001), GG vs. CC (OR, 5.51; 95% CI, 2.06-14.79; *P* = 0.001), CG vs. CC (OR, 2.01; 95% CI, 1.44-2.82; *P*<0.001) and G vs. C (OR, 2.26; 95% CI, 1.69-3.02; *P*<0.001) (**Table 4**).

Tests for publication bias

We used Begg's Funnel plot and Egger's test to examine publication bias of included studies. No statistical evidence of publication bias was identified in all genetic models (G vs. C: Begg's test *P* = 0.709, Egger's test *P* = 0.202; GG vs. CC: Begg's test *P* = 0.879, Egger's test *P* = 0.935; CG vs. CC: Begg's test *P* = 0.372, Egger's test *P* = 0.168; GG+CG vs. CC: Begg's test *P* = 0.380, Egger's test *P* = 0.157; GG vs. CG+CC: Begg's test *P* = 1.000, Egger's test *P* = 0.676; **Figure 3**).

Sensitivity analyses

Influence of the potential publication bias involved in the meta-analysis on the pooled ORs and CIs was assessed by non-parametric "trim-and-fill" method and the filling of any potential studies did not significantly altered the final decision, suggesting that our results were stable and statistically robust: GG+CG vs. CC (adjusted pooled OR, 0.971; 95% CI, 0.897-1.051; *P* = 0.464), GG vs. CG+CC (adjusted pooled OR, 1.025; 95% CI, 0.865-1.213; *P* = 0.779), GG vs. CC (adjusted pooled OR, 1.002; 95% CI, 0.835-1.203; *P* = 0.982), CG vs. CC (adjusted pooled OR, 0.975; 95% CI, 0.905-1.051; *P* = 0.506) and G vs. C (adjusted pooled OR, 0.982; 95% CI, 0.911-1.059; *P* = 0.641) (**Figure 4**).

Tests for heterogeneity

Heterogeneity was assessed by the χ^2-based Q-test in overall genetic models and sub-group analyses. We explored the main source of heterogeneity in sub-group analyses of ethnicity and cancer type. In current study, Caucasians, mixed populations, breast cancer, pancreatic cancer and prostate cancer provided potential sources of heterogeneity.

Discussion

The *PPARG* rs1801282 C>G polymorphism has been popularly examined on the risk of many

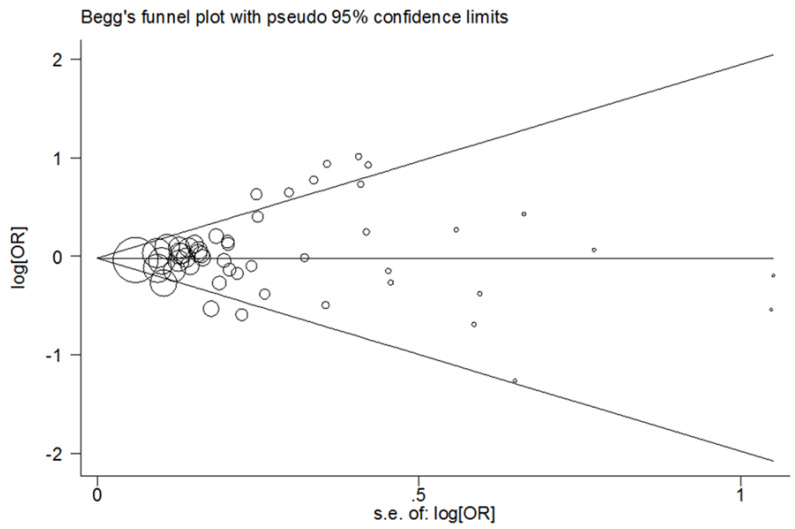

Figure 3. For *PPARG* rs1801282 C>G polymorphism, Begg's funnel plot analysis for publication bias (allele comparing model).

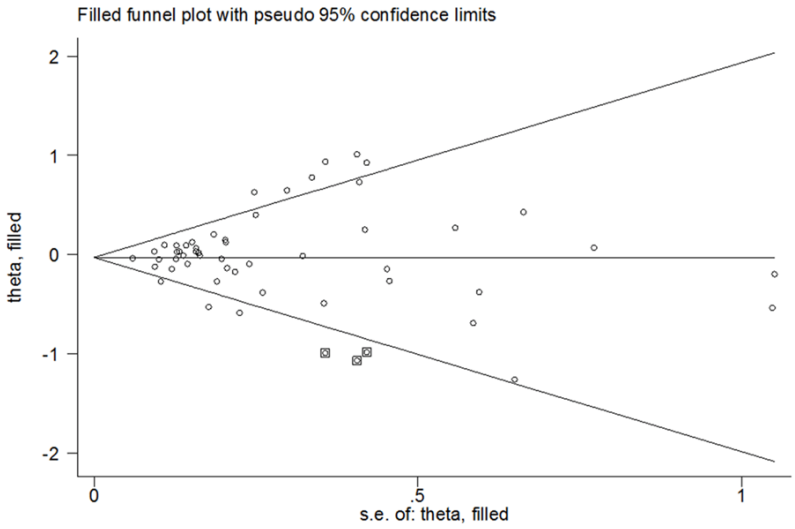

Figure 4. For *PPARG* rs1801282 C>G polymorphism, Filled funnel plot of meta-analysis (allele comparing model).

cancers; however, the results of such studies are inconsistent. To address the gap, we performed an updated meta-analysis of published studies. The results indicated that *PPARG* rs1801282 C>G was not associated with the risk of overall cancer. The results from our sub-group analyses suggested that there was an effective modification of the cancer risk among Asians and gastric cancer patients.

Accumulating evidences demonstrated that the *PPARG* gene is related to malignance, which plays an important role in the pathogenesis of multiple cancers in some clinical studies and animal models. The association between *PPARG* rs18012-82 C>G polymorphism and cancer risk has been widely explored. The prior study reported that *PPARG* rs1-801282 C>G polymorphism was associated with reduced transactivation activity, lower body mass index and improved insulin sensitivity among middle-aged and elderly Caucasians [3]. *PPARG* gene variants may increase susceptibility of colorectal cancer by interruption of the metabolism of a high fat diet [53]. In the current study, a significantly increased risk of cancer correlated with *PPARG* rs1801282 C>G polymorphism was overt among Asians and gastric cancer patients. Our results suggest different cancerigenic mechanisms of different cancers and different population. A previous meta-analysis was performed to determine the effect of *PPARG* polymorphisms on the risk of cancer [15]. Comparing with that, our pooled analyses have some merits. First, this is a larger samples meta-analysis not only to analyze the association between *PPARG* rs1801282 C>G and cancer susceptibility in different races and different cancer types, but also to support the rs1801282 C>G polymorphism is a risk factor in Asians and gastric cancer. Second, we carried out a more extensively pooled analysis by calculating five different comparison models and performing sub-group analyses.

Since heterogeneity across studies may affect the strengths of results, we conducted sub-group analyses. In our study, relatively high heterogeneity was observed. Then, the random-

effect model was utilized when significant heterogeneity was found. Meanwhile, to analyze the major source of heterogeneity, we conducted sub-group analyses by races and cancer types. Results of meta-analysis showed that heterogeneity greatly reduced or vanished in some sub-groups. We also performed non-parametric "trim-and-fill" method to verify the stability of our results. The adjusted ORs and CIs were not materially altered, suggesting that the results of our study were reliable and suggestive. The publication bias across studies for the correlation of *PPARG* rs1801282 C>G polymorphism with cancer risk was not observed.

Some limitations should be noted in this meta-analysis when interpreting the results. First of all, only published literatures were included in our study, some unpublished investigations that might also be fit for the inclusion criteria were ignored. Secondly, due to limited individual data (e.g., age, sex and other environmental factors) in some studies, we did not perform a more precise analysis, which limited further assessments to a certain extent. Finally, in some subgroups, sample sizes were relatively small, which might have insufficient power to get a reliable result. In the future, studies with larger sample sizes will be needed to validate these associations.

In conclusion, our findings suggest that *PPARG* rs1801282 C>G polymorphism is a candidate for susceptibility to gastric cancer and Asians. Further studies with larger samples and detailed environmental factors will be needed to confirm our results.

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Disclosure of conflict of interest

None.

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