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Original Article

Cyclooxygenase-2 -1195G>A (rs689466) polymorphism and cancer susceptibility: an updated meta-analysis involving 50,672 subjects

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Abstract: The association between *cyclooxygenase-2* (*COX-2*) -1195G>A (rs689466) polymorphism and cancer risk has been extensively explored. However, the results of previous studies remain controversial. To address this gap, we performed an updated meta-analysis of fifty-eight studies involving a total of 50,672 subjects. Searching of PubMed and Embase databases was performed for publications on the association between *COX-2* -1195G>A polymorphism and the risk of cancer. Statistical correlation was identified between *COX-2* -1195G>A variants and overall cancer risk in five genetic models. In a sub-group analysis based on cancer type, significant association between *COX-2* -1195G>A polymorphism and increased risk of gastric cancer, pancreatic cancer, hepatocellular carcinoma and other cancers was found. In a sub-group analysis by ethnicity, increased cancer risk was observed among Asians instead of Caucasians, Africans and mixed populations. Furthermore, in a sub-group analysis based on cancer system, increased cancer risk was found in digestive system cancer and other system cancer. Non-parametric "trim-and-fill" method was harnessed as a sensitivity analysis method and the results suggested our findings reliable. In summary, the results of our meta-analysis highlight that *COX-2* -1195G>A polymorphism may be a risk factor for cancer.

Keywords: Cancer, gene polymorphism, cyclooxygenase-2, meta-analysis

Introduction

Accumulating evidence demonstrates that carcinogenesis is a multi-step and multi-factorial process that results from complex interactions of both environmental and genetic factors. The pathogenesis of malignance is very complicated and has not been clarified completely, although recent studies have kept a watchful eye on the role of the chronic infection and immune system [1, 2]. Recently, evidence highlights that inflammatory factors of chronic infection may have a hand in the development of multiple cancers by mediating immune suppression, suppressing apoptosis and promoting cell proliferation [3-5]. For this reason, chronic infection is increasing as a hot spot in clinical and experimental cancer research [6, 7].

Inflammatory factors of chronic infection have long been considered as a risk candidate for multiple human malignances [8-11]. Of late, Wang reported that the modifiable risk factors elucidate nearly 60% of cancer related deaths in China, with a prominent role of tobacco consumption and chronic infection [12].

Cyclooxygenase-2 (COX-2), an inducible enzyme, converts arachidonic acid to prostaglandins which are the effective mediators of inflammation reaction. It is reported that COX-2 is over-expressed in tumor tissue specimens, whereas in normal tissue, its expression is often undetectable [13, 14]. Previous clinical and experimental investigation suggested that COX-1/-2 inhibitor attenuates the risk of carcinoma [15].

Of late, the association between *COX-2* -1195G >A (rs689466) and cancer risk was extensively explored. Previous studies supported that *COX-2* -1195G>A was associated with increased risk of overall cancer, especially in non-nonsteroidal anti-inflammatory drug users [16-18]. Recently, more investigations were performed to validate this potential correlation. Up to now, fifty-eight studies focus on the association of *COX-2* -1195G>A polymorphism with malignance, and the results remain conflicting. The aim of our study was to extensively investigate the association between *COX-2* -1195G>A polymorphism and cancer risk by an updated meta-analysis.

Materials and methods

Search strategy

All publications investigating the association between *COX-2* -1195G>A and cancer risk were identified by exhausted electronic literature searches of PubMed and Embase databases (published up to July 31, 2014) with search terms of 'COX2', 'COX-2', 'Cyclooxygenase-2', 'Cyclooxygenase 2', 'rs689466', 'polymorphism', 'mutation', 'locus', 'SNP', 'neoplasm', 'carcinoma', 'cancer', 'tumor', and 'malignance'. Additionally, in searching, no language was restricted. The citations in retrieved publications, published reviews, comments and letters were also scanned for relevant publications.

Inclusion and exclusion criteria

Included studies had to meet the following criteria: 1) they should be case-control or cohort study design; 2) they should focus on the association between *COX-2* -1195G>A polymorphism and cancer; 3) they should supply the available frequencies of genotypes or alleles; 4) genotype distributions among controls were consistent with Hardy-Weinberg equilibrium (HWE). The major exclusion criteria were: 1) no usable data reported; 2) overlapping data; 3) only relevant to oncotherapy; not case-control study or cohort study design; 5) comment, review, editorial, meta-analysis or letter.

Data extraction

In a standardized form, three researchers (Y. Wang, H. Jiang and T. Liu) extracted the data independently and the following items were extracted: the first author's last name, year of publication, cancer type, country, populations, genotype frequencies and sample size (total cases and controls), genotype method. When we meet conflicting evaluations, differences were adjudicated and reached a consensus on all of the items after discussion among all reviewers.

Statistical analysis

Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to evaluate the strength of association between *COX-2* -1195G>A polymorphism and cancer risk. The pooled ORs were conducted for five genetic models including allele comparing model (A vs. G), dominant model (AA+GA vs. GG), recessive model (AA vs. GA+GG), heterozygote comparison (GA vs. GG) and homozygote comparison (AA vs. GG). $P < 0.05$ (two tailed) was defined as statistically significant. We also performed stratification analyses by cancer type (any cancer type < 3 individual case-control studies was defined as 'other cancers'), ethnicity and system. Heterogeneity was calculated by a chi square-based Q statistical and I^2 test. Statistical significance was considered at $P < 0.1$ or $I^2 > 50\%$ and a random effect model (the DerSimonian-Laird method) was used [19], otherwise a fixed-effect model (the Mantel-Haenszel method) was applied [20]. A web-based HWE program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) was harnessed to assess the evidence of HWE in controls. The potential publication bias was measured by the Begg's funnel plot and Egger's test. The statistical significance level was set at 0.05. Nonparametric "trim-and-fill" method was used to determine the stability of our results. All the statistical manipulations were performed using STATA (Version 12.0) statistical software (Stata Corp LP, College Station, Texas).

Results

Studies characteristics

A total of 959 relevant publications were retrieved from electronic literature searches. The detailed selecting process was presented in **Figure 1**. In some publications, there were more than two independent groups, which were treated separately as individual studies [21-26]. Lastly, fifty-eight studies on the associa-

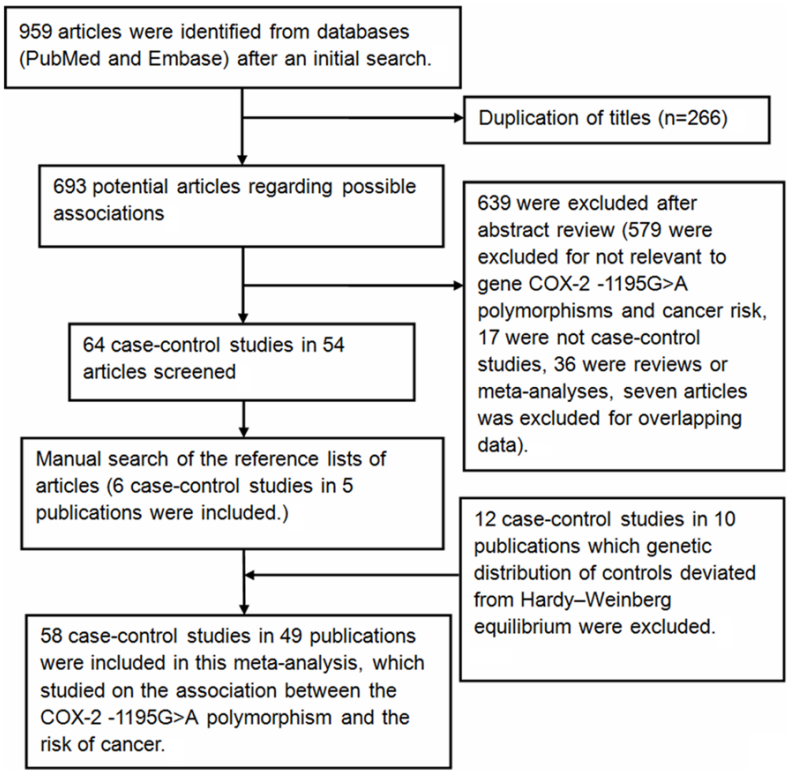

Figure 1. Flow diagram showing the study selection procedure in meta-analysis.

tion of *COX-2* -1195G>A polymorphism with cancer risk were pooled [22, 27-57]. Among them, eleven investigated colorectal cancer [21, 26, 34, 55, 58-60], eight investigated esophageal cancer [22, 43, 44, 46, 61, 62], six investigated hepatocellular carcinoma [33, 38, 42, 50, 63, 64], five investigated prostate cancer [29, 36, 57, 65], four investigated gastric cancer [31, 32, 52, 53], four investigated lymphoma [24, 56], four investigated breast cancer [27, 51, 54, 66], three investigated pancreatic cancer [47, 48, 67], and the others investigated gallbladder cancer [45], bladder cancer [30, 37], head and neck cancer [28, 68], leukemia [35, 39], lung cancer [41, 69], skin cancer [70, 71] and oral cancer [40, 49]. With respect to subjects, twenty-seven were Asians [27-53], twenty-five were Caucasians [21, 24, 26, 57-71], four were mixed populations [22, 54-56] and two were Africans [22, 57]. **Table 1** gives characteristics and **Table 2** gives *COX-2* -1195G>A genotype and allele frequencies.

Meta-analysis results

In total, 50,672 subjects (19,947 cases and 30,725 controls) were relevant to the association between *COX-2* -1195G>A and cancer risk. Overall, significantly increased cancer risk was associated with the *COX-2* -1195A allele: dominant model comparison AA+GA vs. GG (OR, 1.14; 95% CI, 1.04-1.25; P = 0.007), recessive model comparison AA vs. GA+GG (OR, 1.11; 95% CI, 1.04-1.18; P = 0.003), homozygote comparison AA vs. GG (OR, 1.21; 95% CI, 1.07-1.36; P = 0.002), heterozygote comparison GA vs. GG (OR, 1.09; 95% CI, 1.00-1.18; P = 0.045) and allele comparison A vs. G (OR, 1.09; 95% CI, 1.03-1.15; P = 0.002) (**Table 3**). In a sub-group analysis based on cancer type, the association between *COX-2* -1195G>A polymorphism and an increased risk of gastric cancer was identified in five genetic models: AA+GA vs. GG (OR, 1.43; 95% CI, 1.15-1.76; P = 0.001), AA vs. GA+GG (OR, 1.36; 95% CI, 1.02-1.81; P = 0.036), AA vs. GG (OR, 1.72; 95% CI, 1.35-2.20; P < 0.001), GA vs. GG (OR, 1.28; 95% CI, 1.02-1.60; P = 0.031) and A vs. G (OR, 1.30; 95% CI, 1.16-1.47; P < 0.001), of pancreatic cancer in five genetic models: AA+GA vs. GG (OR, 1.66; 95% CI, 1.12-2.48; P = 0.012), AA vs. GA+GG (OR, 1.93; 95% CI, 1.14-3.30; P = 0.015), AA vs. GG (OR, 2.36; 95% CI, 1.27-4.40; P = 0.007), GA vs. GG (OR, 1.30; 95% CI, 1.04-1.62; P = 0.022) and A vs. G (OR, 1.66; 95% CI, 1.11-2.47; P = 0.013), of hepatocellular carcinoma in one genetic model: AA vs. GG (OR, 1.43; 95% CI, 1.02-2.00; P = 0.039) and of other cancers in two genetic models: AA vs. GA+GG (OR, 1.14; 95% CI, 1.03-1.25; P = 0.009) and A vs. G (OR, 1.09; 95% CI, 1.02-1.16; P = 0.011) (**Table 4**). In a sub-group analysis by ethnicity, our results confirmed that *COX-2* -1195A allele was associated with an increased cancer risk in Asians: AA+GA vs. GG (OR, 1.22; 95% CI, 1.10-1.34; P < 0.001), AA vs. GA+GG (OR, 1.23; 95% CI, 1.12-1.35; P < 0.001), AA vs. GG (OR, 1.36; 95% CI, 1.20-1.55; P < 0.001), GA vs. GG (OR, 1.15; 95% CI, 1.05-

Table 1. Characteristics of studies in the meta-analysis

Study	Publication year	Ethnicity	Country	Cancer type	Sample size (case/control)	Genotype method
Moatter et al.	2014	Asians	Pakistan	breast cancer	150/101	PCR-RFLP
Gharib et al.	2014	Caucasians	Egypt	hepatocellular carcinoma	120/130	PCR-RFLP
Niu et al.	2014	Asians	China	head and neck cancer	260/1047	TaqMan
Sugie et al.	2014	Asians	Japan	prostate cancer	134/86	PCR-RFLP
Pereira et al.	2014	Caucasians	Portugal	colorectal cancer	246/480	MassARRAY iPLEX Gold technology
Chang et al.	2013	Asians	China	bladder cancer	375/375	PCR-RFLP
Andersen et al.	2013	Caucasians	Denmark	colorectal cancer	970/1789	KASP™ genotyping assay
Makar et al.	2013	Caucasians	USA	colorectal cancer	1470/1837	Illumina™ GoldenGate
Makar et al.	2013	Caucasians	USA	colorectal cancer	583/775	Illumina™ GoldenGate
Makar et al.	2013	Caucasians	USA	colorectal cancer	959/1535	Illumina™ GoldenGate
Makar et al.	2013	Caucasians	USA	colorectal cancer	505/839	Illumina™ GoldenGate
Kopp et al.	2013	Caucasians	Denmark	prostate cancer	334/334	RT-PCR
Shin et al.	2012	Asians	Korea	gastric cancer	100/100	PCR-RFLP
Li et al.	2012	Asians	China	gastric cancer	296/319	PCR-RFLP
Chang et al.	2012	Asians	China	hepatocellular carcinoma	298/298	PCR-RFLP
Zhang et al.	2012	Asians	China	colorectal cancer	343/340	PCR-RFLP
Talar-Wojnarowska et al.	2011	Caucasians	Poland	pancreatic cancer	85/116	PCR-RFLP
Bye et al.	2011	Africans	South Africa	esophageal cancer	358/477	TaqMan
Bye et al.	2011	mixed	South Africa	esophageal cancer	201/427	TaqMan
Zheng et al.	2011	Asians	China	leukemia	446/725	PCR-RFLP
Wu et al.	2011	Asians	China	prostate cancer	218/436	PCR-RFLP
Akkiz et al.	2011	Caucasians	Turkey	hepatocellular carcinoma	129/129	PCR-RFLP
Brasky et al.	2011	Caucasians	USA	breast cancer	1077/1910	RT-PCR
Gangwar et al.	2011	Asians	India	bladder cancer	212/250	PCR-RFLP
Fan et al.	2011	Asians	China	hepatocellular carcinoma	780/780	TaqMan
Piranda et al.	2010	mixed	Brazil	breast cancer	318/273	PCR-RFLP
Wang et al.	2010	Asians	China	leukemia	266/266	PCR-RFLP
Mittal et al.	2010	Asians	India	oral cancer	193/137	PCR-RFLP
Liu et al.	2010	Asians	China	lung cancer	358/716	PCR-RFLP
Liu et al.	2010	Asians	China	hepatocellular carcinoma	210/210	PCR–RFLP
Chen et al.	2009	Asians	China	esophageal cancer	188/324	PCR-RFLP
Hoff et al.	2009	Caucasians	The Netherlands	colorectal cancer	326/369	PCR-RFLP
Kristinsson et al.	2009	Caucasians	The Netherlands	esophageal cancer	174/240	PCR-RFLP

Kristinsson et al.	2009	Caucasians	The Netherlands	esophageal cancer	70/240	PCR-RFLP
Hu et al.	2009	Asians	China	esophageal cancer	180/194	PCR-RFLP
Srivastava et al.	2009	Asians	India	gallbladder cancer	167/184	PCR-RFLP
Thompson et al.	2009	mixed	USA	colorectal cancer	422/481	Taqman
Upadhyay et al.	2009	Asians	India	esophageal cancer	174/216	PCR-RFLP
Zhao et al.	2009	Asians	China	pancreatic cancer	393/786	PCR-RFLP
Peters et al.	2009	Caucasians	The Netherlands	head and neck cancer	431/438	PCR-RFLP
Chang et al.	2009	mixed	USA	lymphoma	473/373	TaqMan
Xu et al.	2008	Asians	China	pancreatic cancer	283/566	PCR-RFLP
Chiang et al.	2008	Asians	China	oral cancer	377/442	PCR-RFLP
Vogel et al.	2008	Caucasians	Denmark	lung cancer	403/744	TaqMan
Hoeft et al.	2008	Caucasians	Germany	lymphoma	554/710	TaqMan
Hoeft et al.	2008	Caucasians	Germany	lymphoma	35/710	TaqMan
Hoeft et al.	2008	Caucasians	Germany	lymphoma	116/710	TaqMan
Xu et al.	2008	Asians	China	hepatocellular carcinoma	270/540	PCR-RFLP
Cheng et al.	2007	Africans	USA	prostate cancer	89/506	Taqman
Cheng et al.	2007	Caucasians	USA	prostate cancer	417/506	Taqman
Moons et al.	2007	Caucasians	The Netherlands	esophageal cancer	140/240	PCR-RFLP
Lira et al.	2007	Caucasians	Italy	skin cancer	107/133	PCR-RFLP
Gao et al.	2007	Asians	China	breast cancer	615/643	PCR-RFLP
Vogel et al.	2007	Caucasians	Denmark	skin cancer	322/322	Taqman
Jiang et al.	2007	Asians	China	gastric cancer	254/304	PCR-RFLP
Siezen et al.	2006	Caucasians	Netherlands	colorectal cancer	204/399	PCR-RFLP
Siezen et al.	2006	Caucasians	Netherlands	colorectal cancer	304/373	PCR-RFLP
Liu et al.	2006	Asians	China	gastric cancer	248/1523	DHPLC

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; DHPLC: denaturing high-performance liquid chromatography analysis.

Table 2. COX-2 -1195G>A polymorphism genotype distribution and allele frequency

Study	Publication year	Case			Control			Case		Control		HWE
		GG	GA	AA	GG	GA	AA	A	G	A	G	
Moatter et al.	2014	4	19	112	3	21	77	243	27	175	27	0.304270
Gharib et al.	2014	17	60	43	31	66	33	146	94	132	128	0.858603
Niu et al.	2014	61	126	72	222	542	271	270	248	1084	986	0.109869
Sugie et al.	2014	21	61	52	20	47	19	165	103	85	87	0.387570
Pereira et al.	2014	15	85	143	16	133	323	371	115	779	165	0.614121
Chang et al.	2013	89	181	105	97	171	107	391	359	385	365	0.090733
Andersen et al.	2013	47	313	587	61	560	1126	1487	407	2812	682	0.397081
Makar et al.	2013	57	455	910	67	509	1198	2275	569	2905	643	0.162224
Makar et al.	2013	20	185	376	29	237	509	937	225	1255	295	0.828845
Makar et al.	2013	33	287	619	63	496	958	1525	353	2412	622	0.904941
Makar et al.	2013	21	138	338	20	249	558	814	180	1365	289	0.205656
Kopp et al.	2013	13	111	210	12	112	210	531	137	532	136	0.533685
Shin et al.	2012	14	54	32	22	41	37	118	82	115	85	0.107125
Li et al.	2012	53	145	98	80	166	73	341	251	312	326	0.461235
Chang et al.	2012	70	144	84	74	145	81	312	284	307	293	0.569879
Zhang et al.	2012	50	216	77	94	184	62	370	316	308	372	0.089719
Talar-Wojnarowska et al.	2011	13	26	46	44	48	24	118	52	96	136	0.113223
Bye et al.	2011	0	44	301	1	47	417	646	44	881	49	0.786975
Bye et al.	2011	0	40	154	9	112	298	348	40	708	130	0.686305
Zheng et al.	2011	100	222	124	176	365	184	470	422	733	717	0.850095
Wu et al.	2011	57	100	61	104	210	122	222	214	454	418	0.464218
Akkiz et al.	2011	2	36	91	2	32	95	218	40	222	36	0.707524
Brasky et al.	2011	34	271	660	54	471	1199	1591	339	2869	579	0.353199
Gangwar et al.	2011	162	48	2	182	64	4	52	372	72	428	0.543520
Fan et al.	2011	204	390	186	205	381	194	762	798	769	791	0.522773
Piranda et al.	2010	3	62	224	3	51	190	510	68	431	57	0.838274
Wang et al.	2010	63	128	75	65	127	74	278	254	275	257	0.472808
Mittal et al.	2010	3	57	133	5	32	100	323	63	232	42	0.241040
Liu et al.	2010	84	172	102	178	345	193	376	340	731	701	0.336883
Liu et al.	2010	31	110	69	52	108	50	248	172	208	212	0.677855
Chen et al.	2009	42	88	58	57	165	102	204	172	369	279	0.487719
Hoff et al.	2009	12	101	213	13	124	232	527	125	588	150	0.470706
Kristinsson et al.	2009	15	59	100	6	80	154	259	89	388	92	0.240585
Kristinsson et al.	2009	5	26	39	6	80	154	104	36	388	92	0.240585
Hu et al.	2009	39	80	61	50	103	41	202	158	185	203	0.371617
Srivastava et al.	2009	104	52	11	142	37	5	74	260	47	321	0.185970
Thompson et al.	2009	9	138	275	15	168	297	688	156	762	198	0.130845
Upadhyay et al.	2009	126	46	2	168	45	3	50	298	51	381	0.994569
Zhao et al.	2009	85	194	114	212	401	173	422	364	747	825	0.521326
Peters et al.	2009	22	134	275	15	163	260	684	178	683	193	0.081594
Chang et al.	2009	19	124	314	13	99	249	752	162	597	125	0.422989
Xu et al.	2008	58	143	82	154	284	128	307	259	540	592	0.892966
Chiang et al.	2008	80	187	101	114	235	93	389	347	421	463	0.166848
Vogel et al.	2008	17	124	262	24	253	467	648	158	1187	301	0.143186
Hoeft et al.	2008	14	147	361	19	197	447	869	175	1091	235	0.627123
Hoeft et al.	2008	1	13	19	19	197	447	51	15	1091	235	0.627123
Hoeft et al.	2008	1	33	76	19	197	447	185	35	1091	235	0.627123
Xu et al.	2008	52	125	93	119	287	134	311	229	555	525	0.138287
Cheng et al.	2007	2	20	67	0	12	77	154	24	166	12	0.495255
Cheng et al.	2007	13	134	270	15	122	280	674	160	682	152	0.705855
Moons et al.	2007	3	54	83	10	76	154	220	60	384	96	0.871799
Lira et al.	2007	3	25	76	2	33	96	177	31	225	37	0.658979
Gao et al.	2007	121	305	175	150	327	166	655	547	659	627	0.652871

Vogel et al.	2007	10	95	199	15	121	179	493	115	479	151	0.338448
Jiang et al.	2007	48	132	74	62	163	79	280	228	321	287	0.186688
Siezen et al.	2006	10	59	127	20	128	243	313	79	614	168	0.557997
Siezen et al.	2006	19	132	283	41	226	422	698	170	1070	308	0.148689
Liu et al.	2006	44	116	88	377	771	375	292	204	1521	1525	0.626310

HWE: Hardy-Weinberg equilibrium.

Table 3. Meta-analysis of *COX-2* -1195G>A polymorphisms and cancer risk in a sub-group analysis by race

Genetic comparison	Population	OR (95% CI); *P*	Test of heterogeneity	
			(*p*-Value, I^2)	Model
AA+GA vs. GG	All	1.14 (1.04-1.25); 0.007	< 0.001, 43.4%	R
	Asians	1.22 (1.10-1.34); < 0.001	0.014, 41.4%	R
	Caucasians	0.97 (0.80-1.17); 0.716	0.009, 44.6%	R
	Africans	0.58 (0.09-3.61);0.556	0.280, 14.4%	F
	Mixed	1.28 (0.79-2.08); 0.321	0.378, 2.9%	F
AA vs. GA+GG	All	1.11 (1.04-1.18); 0.003	< 0.001, 56.5%	R
	Asians	1.23 (1.12-1.35); < 0.001	0.024, 38.3%	R
	Caucasians	1.02 (0.93-1.12); 0.660	< 0.001, 58.6%	R
	Africans	0.69 (0.48-1.01); 0.058	0.265, 19.7%	F
	Mixed	1.13 (0.96-1.33); 0.148	0.294, 19.2%	F
AA vs. GG	All	1.21 (1.07-1.36); 0.002	< 0.001, 54.4%	R
	Asians	1.36 (1.20-1.55); < 0.001	0.006, 45.6%	R
	Caucasians	0.99 (0.79-1.24); 0.940	< 0.001, 57.9%	R
	Africans	0.54 (0.09-3.31); 0.501	0.263, 20.0%	F
	Mixed	1.31 (0.81-2.14); 0.273	0.338, 10.9%	F
GA vs. GG	All	1.09 (1.00-1.18); 0.045	0.073, 22.2%	R
	Asians	1.15 (1.05-1.26); 0.003	0.085, 28.5%	R
	Caucasians	0.94 (0.82-1.08); 0.375	0.281, 12.8%	F
	Africans	0.89 (0.13-6.02); 0.903	0.348, 0.0%	F
	Mixed	1.22 (0.73-2.02); 0.451	0.513, 0.0%	F
A vs. G	All	1.09 (1.03-1.15); 0.002	< 0.001, 63.9%	R
	Asians	1.17 (1.10-1.25); < 0.001	0.001, 51.0%	R
	Caucasians	1.02 (0.93-1.11); 0.720	< 0.001, 66.1%	R
	Africans	0.70 (0.49-1.01); 0.056	0.186, 42.7%	F
	Mixed	1.12 (0.97-1.30); 0.115	0.170, 40.3%	F

F indicates fixed model; R indicates random model.

1.26; *P* = 0.003) and A vs. G (OR, 1.17; 95% CI, 1.10-1.25; *P* < 0.001), a borderline decreased cancer risk was identified in two genetic models: AA vs. GA+GG (OR, 0.69; 95% CI, 0.48-1.01; *P* = 0.058) and A vs. G (OR, 0.70; 95% CI, 0.49-1.01; *P* = 0.056) in Africans, but not in Caucasians or mixed populations (**Table 3**; **Figure 2**). Additionally, in a sub-group analysis based on cancer system, a significant increased risk of digestive system cancer was confirmed in five genetic models: AA+GA vs. GG (OR, 1.22; 95% CI, 1.06-1.39; *P* = 0.004), AA vs. GA+GG (OR, 1.14; 95% CI, 1.04-1.26; *P* = 0.008), AA vs. GG (OR, 1.31; 95% CI, 1.10-1.57; *P* = 0.003), GA vs. GG (OR, 1.15; 95% CI, 1.02-1.30; *P* = 0.018) and A vs. G (OR, 1.13; 95% CI, 1.04-1.22; *P* = 0.003) and of other system cancer in one genetic model: AA vs. GA+GG (OR, 1.21; 95% CI, 1.02-1.42; *P* = 0.026) (**Table 5**; **Figure 3**).

Publication bias

Results of Funnel plots and the Egger's test indicated that there was no publication bias in this meta-analysis (A vs. G: Begg's test *P* = 0.872, Egger's test *P* = 0.372; AA vs. GG: Begg's test *P* = 0.862, Egger's test *P* = 0.981; GA vs. GG: Begg's test *P* = 0.872, Egger's test *P* = 0.908; AA+GA vs. GG: Begg's test *P* = 0.995, Egger's test *P* = 0.875; AA vs. GA+GG: Begg's test *P* = 0.717, Egger's test *P* = 0.088; **Figure 4**).

Sensitivity analyses

Nonparametric "trim-and-fill" method was performed to determine the reliability of our results. The adjusted ORs and CIs were not qualitatively altered, which demonstrated *COX-2* -1195G>A polymorphism might be a risk factor for overall cancer risk (A vs. G: adjusted pooled OR = 1.09, 95% CI: 1.03-1.15, *P* = 0.002; AA vs. GG: adjusted pooled OR = 1.21, 95% CI: 1.07-1.36, *P* = 0.002; AA+GA vs. GG: adjusted pooled OR = 1.14, 95% CI: 1.04-1.25, *P* = 0.007; AA vs. GA+GG: adjusted pooled OR = 1.09, 95% CI: 1.02-1.18, *P* = 0.014; GA vs. GG:

Table 4. Meta-analysis of *COX-2* -1195G>A polymorphisms and cancer risk in a sub-group analysis by cancer type

Genetic comparison	Cancer type	OR (95% CI); *P*	Test of heterogeneity	
			(*p*-Value, I^2)	Model
AA+GA vs. GG	All	1.14 (1.04-1.25); 0.007	< 0.001, 43.4%	R
	Breast cancer	1.11 (0.88-1.39); 0.374	0.700, 0.0%	F
	Hepatocellular carcinoma	1.16 (0.99-1.36); 0.060	0.169, 35.7%	F
	Prostate cancer	1.00 (0.76-1.33); 0.984	0.453, 0.0%	F
	Colorectal cancer	1.03 (0.78-1.36); 0.848	0.001, 65.6%	R
	Gastric cancer	1.43 (1.15-1.76); 0.001	0.568, 0.0%	F
	Pancreatic cancer	1.66 (1.12-2.48); 0.012	0.054, 65.8%	R
	Esophageal cancer	0.91 (0.56-1.47); 0.697	0.013, 60.5%	R
	Lymphoma	1.07 (0.67-1.70); 0.776	0.682, 0.0%	F
	Other cancers	1.08 (0.96-1.21); 0.179	0.158, 28.5%	F
AA vs. GA+GG	All	1.11 (1.04-1.18); 0.003	< 0.001, 56.5%	R
	Breast cancer	1.03 (0.90-1.17); 0.665	0.316, 15.1%	F
	Hepatocellular carcinoma	1.22 (0.96-1.54); 0.100	0.040, 57.1%	R
	Prostate cancer	1.01 (0.74-1.36); 0.962	0.031, 62.3%	R
	Colorectal cancer	1.00 (0.91-1.11); 0.926	0.030, 49.9%	R
	Gastric cancer	1.36 (1.02-1.81); 0.036	0.076, 56.3%	R
	Pancreatic cancer	1.93 (1.14-3.30); 0.015	0.002, 83.3%	R
	Esophageal cancer	1.00 (0.76-1.31); 0.989	0.013, 60.8%	R
	Lymphoma	1.02 (0.86-1.21); 0.795	0.608, 0.0%	F
	Other cancers	1.14 (1.03-1.25); 0.009	0.601, 0.0%	F
AA vs. GG	All	1.21 (1.07-1.36);0.002	< 0.001, 54.4%	R
	Breast cancer	1.14 (0.88-1.47); 0.316	0.551, 0.0%	F
	Hepatocellular carcinoma	1.43 (1.02-2.00); 0.039	0.032, 59.2%	R
	Prostate cancer	1.08 (0.79-1.48); 0.619	0.156, 39.9%	F
	Colorectal cancer	1.02 (0.78-1.35); 0.880	0.003, 62.7%	R
	Gastric cancer	1.72 (1.35-2.20); < 0.001	0.336, 11.3%	F
	Pancreatic cancer	2.36 (1.27-4.40); 0.007	0.006, 80.4%	R
	Esophageal cancer	0.90 (0.46-1.77); 0.770	0.005, 65.1%	R
	Lymphoma	1.07 (0.67-1.71); 0.761	0.668, 0.0%	F
	Other cancers	1.13 (0.98-1.30); 0.090	0.427, 1.9%	F
GA vs. GG	All	1.09 (1.00-1.18); 0.045	0.073, 22.2%	R
	Breast cancer	1.07 (0.85-1.36); 0.556	0.784, 0.0%	F
	Hepatocellular carcinoma	1.11 (0.94-1.31); 0.201	0.450, 0.0%	F
	Prostate cancer	0.97 (0.72-1.30); 0.837	0.799, 0.0%	F
	Colorectal cancer	1.03 (0.80-1.34); 0.798	0.009, 57.3%	R
	Gastric cancer	1.28 (1.02-1.60); 0.031	0.518, 0.0%	F
	Pancreatic cancer	1.30 (1.04-1.62); 0.022	0.608, 0.0%	F
	Esophageal cancer	0.90 (0.58-1.42); 0.661	0.040, 52.4%	R
	Lymphoma	1.06 (0.66-1.71); 0.812	0.692, 0.0%	F
	Other cancers	1.04 (0.92-1.17); 0.531	0.193, 24.8%	F
A vs. G	All	1.09 (1.03-1.15); 0.002	< 0.001, 63.9%	R
	Breast cancer	1.04 (0.94-1.15); 0.458	0.274, 22.9%	F
	Hepatocellular carcinoma	1.17 (0.99-1.38); 0.057	0.026, 60.7%	R
	Prostate cancer	1.00 (0.79-1.26); 0.976	0.027, 63.5%	R
	Colorectal cancer	1.02 (0.92-1.13); 0.737	0.001, 67.9%	R
	Gastric cancer	1.30 (1.16-1.47); < 0.001	0.209, 33.9%	F
	Pancreatic cancer	1.66 (1.11-2.47); 0.013	< 0.001, 88.1%	R
	Esophageal cancer	0.99 (0.80-1.23); 0.936	0.003, 67.9%	R
	Lymphoma	1.02 (0.88-1.19); 0.752	0.608, 0.0%	F
	Other cancers	1.09 (1.02-1.16); 0.011	0.170, 27.2%	F

F indicates fixed model; R indicates random model.

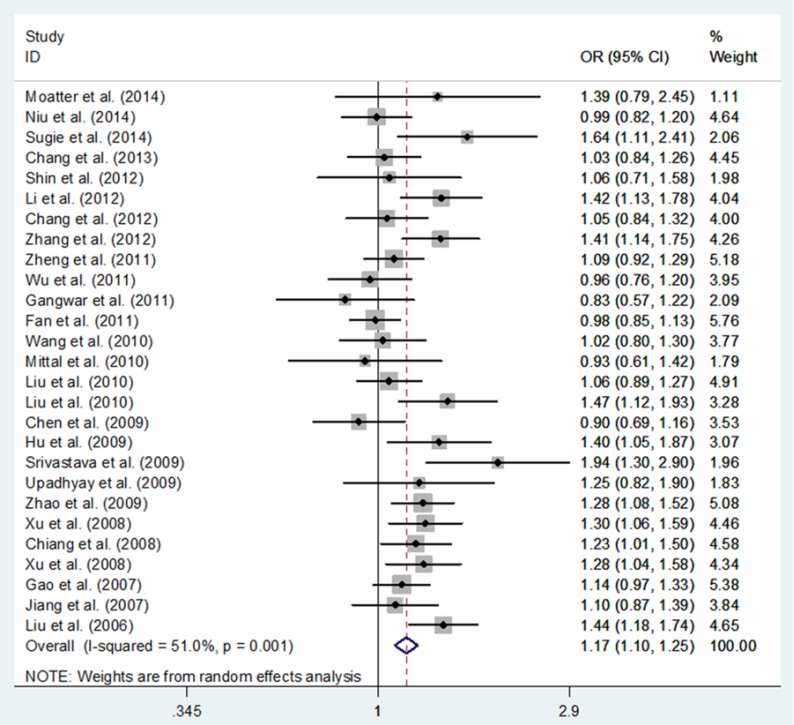

Figure 2. Meta-analysis of *COX-2* -1195G>A polymorphism and cancer risk in Asians: allele comparing model.

adjusted pooled OR = 1.09, 95% CI: 1.00-1.18, *P* = 0.045; **Figure 5**).

Heterogeneity

Significant heterogeneity was obvious in each model among the recruited studies. Sub-group analyses were conducted to explore the source of heterogeneity. The results supported that publications conducted in Asians, Caucasians, colorectal cancer, hepatocellular carcinoma, prostate cancer, gastric cancer, pancreatic cancer, esophageal cancer and digestive system cancer might contribute to the major origin of heterogeneity.

Discussion

In the current meta-analysis, the results indicated that the *COX-2* -1195G>A variants increased cancer risk, especially for gastric cancer, pancreatic cancer, hepatocellular carcinoma and other cancers, such effect was still found in subgroup of digestive system cancer, other system cancer and Asians. Further investigations of the functional interpretation are warranted to comprehend the mechanisms for our results.

The *COX-2* gene is located on chromosome 1q25.2-3 and is composed of ten exons that encode different functional domains. In 5' region, there are several response elements, such as activation protein-2, nuclear factor kB, transforming growth factor, stimulatory protein-1 and cyclic adenosine monophosphate binding sites [72]. Mutation in these regulatory elements might alter gene transcription. As an example, a locus in one of the *COX-2* promoter regions might change binding capacity for certain nuclear proteins, which suggested to be associated with the level of COX-2 expression [72]. A previous report showed that *COX-2* -1195G>A variant modified the transcription of the *COX-2* promoter, leading to several fold greater expression of COX-2 [73]. Combined with our results, these findings demonstrated that the -1195G>A mutation in *COX-2* increased the risk of cancer, perhaps by modifying binding capacity for certain nuclear proteins and promoting the expression of *COX-2* gene.

Since cancer types might affect the findings of meta-analysis, subgroup analysis was carried out. The results highlighted that *COX-2* -1195G>A polymorphism was associated with the risk of gastric cancer, pancreatic cancer, hepatocellular carcinoma and other cancers, but not of esophageal cancer, colorectal cancer, prostate cancer, breast cancer or lymphoma, which was consistent with previous meta-analysis [74-76]. However, these results should be explained with very caution. In some subgroups, only three or four studies were recruited for analysis, which might have insufficient power to obtain a reliable result. Therefore, these correlations need to be further confirmed or refuted in larger size, well-designed studies. Because race could also affect the findings, we conducted subgroup analysis. Our results demonstrated the *COX-2* -1195G>A polymorphism was associated with an increased cancer risk

Table 5. Meta-analysis of *COX-2* -1195G>A polymorphisms and cancer risk in a sub-group analysis by cancer system

Genetic comparison	Cancer system	OR (95% CI); *P*	Test of heterogeneity	
			(*p*-Value, I^2)	Model
AA+GA vs. GG	All	1.14 (1.04-1.25); 0.007	< 0.001, 43.4%	R
	Reproductive and breast cancer	1.11 (0.88-1.39); 0.374	0.700, 0.0%	F
	Digestive system cancer	1.22 (1.06-1.39); 0.004	< 0.001, 57.8%	R
	Urogenital cancer	1.00 (0.83-1.21); 0.999	0.555, 0.0%	F
	hematological malignancy	1.08 (0.88-1.33); 0.445	0.903, 0.0%	F
	Respiratory system cancer	1.01 (0.77-1.33); 0.919	0.320, 0.0%	F
	Other system cancer	0.88 (0.67-1.16); 0.364	0.466, 0.0%	F
AA vs. GA+GG	All	1.11 (1.04-1.18); 0.003	< 0.001, 56.5%	R
	Reproductive and breast cancer	1.03 (0.90-1.17); 0.665	0.316, 15.1%	F
	Digestive system cancer	1.14 (1.04-1.26); 0.008	< 0.001, 68.6%	R
	Urogenital cancer	0.99 (0.79-1.24); 0.923	0.090, 45.3%	R
	hematological malignancy	1.05 (0.92-1.20); 0.487	0.811, 0.0%	F
	Respiratory system cancer	1.09 (0.90-1.32); 0.359	0.915, 0.0%	F
	Other system cancer	1.21 (1.02-1.42); 0.026	0.563, 0.0%	F
AA vs. GG	All	1.21 (1.07-1.36); 0.002	< 0.001, 54.4%	R
	Reproductive and breast cancer	1.14 (0.88-1.47); 0.316	0.551, 0.0%	F
	Digestive system cancer	1.31 (1.10-1.57); 0.003	< 0.001, 67.0%	R
	Urogenital cancer	1.06 (0.83-1.35); 0.624	0.302, 16.8%	F
	hematological malignancy	1.12 (0.89-1.42); 0.343	0.870, 0.0%	F
	Respiratory system cancer	1.03 (0.76-1.41); 0.832	0.353, 0.0%	F
	Other system cancer	0.97 (0.71-1.31); 0.821	0.420, 0.0%	F
GA vs. GG	All	1.09 (1.00-1.18); 0.045	0.073, 22.2%	R
	Reproductive and breast cancer	1.07 (0.85-1.36); 0.556	0.784, 0.0%	F
	Digestive system cancer	1.15 (1.02-1.30); 0.018	0.008, 40.4%	R
	Urogenital cancer	0.99 (0.81-1.22); 0.951	0.819, 0.0%	F
	hematological malignancy	1.06 (0.85-1.32); 0.597	0.917, 0.0%	F
	Respiratory system cancer	0.98 (0.73-1.30); 0.876	0.256, 22.5%	F
	Other system cancer	0.81 (0.61-1.07); 0.143	0.543, 0.0%	F
A vs. G	All	1.09 (1.03-1.15); 0.002	< 0.001, 63.9%	R
	Reproductive and breast cancer	1.04 (0.94-1.15); 0.458	0.274, 22.9%	F
	Digestive system cancer	1.13 (1.04-1.22); 0.003	< 0.001, 74.3%	R
	Urogenital cancer	0.99 (0.84-1.16); 0.871	0.063, 49.8%	R
	hematological malignancy	1.05 (0.95-1.16); 0.370	0.822, 0.0%	F
	Respiratory system cancer	1.05 (0.92-1.21); 0.471	0.891, 0.0%	F
	Other system cancer	1.08 (0.96-1.23); 0.206	0.302, 17.7%	F

F indicates fixed model; R indicates random model.

in Asians but not in Caucasians or mixed populations. While in Africans subgroup, a borderline evidence of association between the *COX-2* -1195G>A polymorphism and cancer risk was identified. Considering only two moderate sample size studies were included and the findings might be due to fluke. Further studies should be performed to confirm the possible effects of *COX-2* -1195G>A polymorphism. In the current meta-analysis, the correlations observed in different system were analyzed as well. The results suggested that *COX-2* -1195G>A polymorphism was associated with the risk of digestive system cancer, which was consistent with previous study [16].

Compared with the previous meta-analyses, some advantages of current study should be

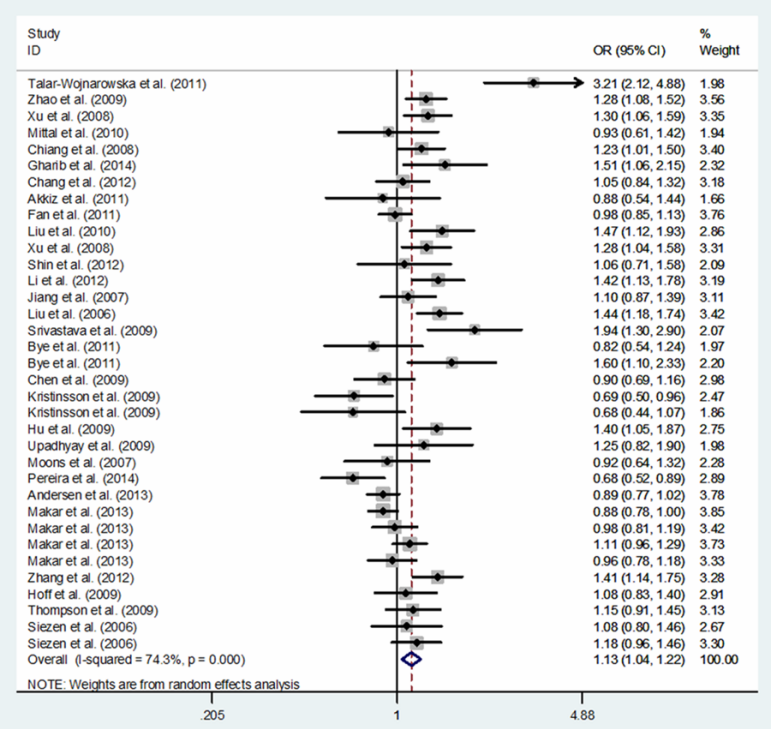

Figure 3. Meta-analysis of *COX-2* -1195G>A polymorphism and cancer risk in digestive cancer system: allele comparing model.

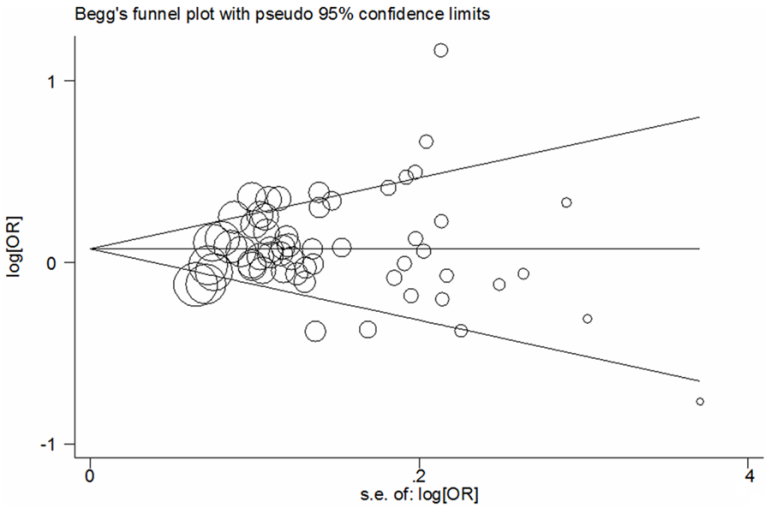

Figure 4. Begg's funnel plot analysis for publication bias in overall cancer: allele comparing model.

adequately addressed. First of all, it updated all eligible data for *COX-2* -1195G>A polymorphism and the risk of cancer. Then, our results corroborated *COX-2* -1195G>A polymorphism effected on pancreatic cancer for the first time. Finally, the methodological issues in pooled analysis (e.g., publication bias, sensitivity and heterogeneity), were all well explored. Although the primary results were stable and suggestive, there were some limitations of this analysis, which should be considered when interpreting the results. First of all, in some subgroup, only two or three eligible case-control studies were recruited; therefore, in these subgroups, the results might be a fluke. For example, in Africans, a borderline evidence of association between the *COX-2* -1195G>A polymorphism and cancer risk was identified. In our study, however, only two studies were included, which might have limited the power to get an accurate result. Second, the eligible studies included only published studies, which might lead to bias, although the statistical data did not show it. Thirdly, large inter-study heterogeneity was observed in overall and some subgroups, which meant explanation of our results, should be very cautious. This could be due to other diversities between investigations, such as gender, age, specified type of cancer, ethnicity variations, smoking, drinking, non-steroidal anti-inflammatory drug use, different lifestyle factors, other environmental risk factors, selection criteria of subjects, and socio-economic factors as well. For lack of access to original data from the reviewed publications, these factors were not considered. Finally, the data of GWAS were not available; the power of the results might be limited.

In conclusion, the investigation of the relationship between *COX-2* -1195G>A polymorphisms and cancer risk is very popular but controversial at present. Our results support that *COX-2* -1195G>A polymorphism is associated with an

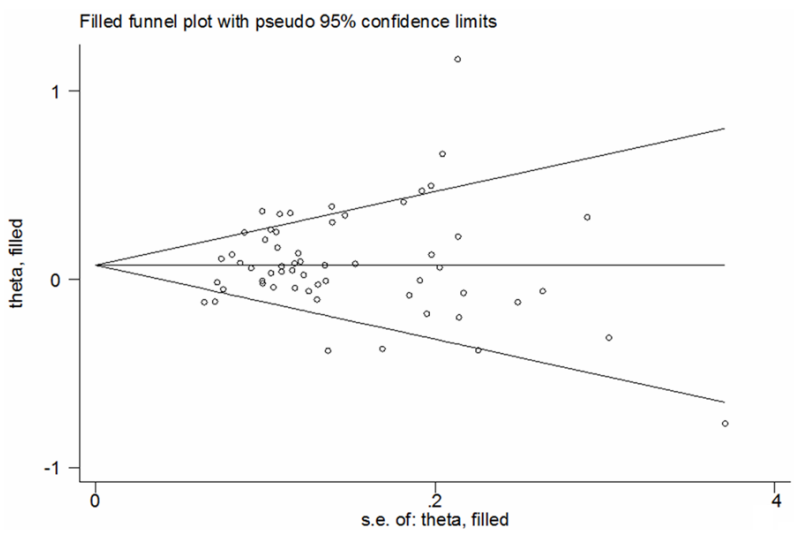

Figure 5. Filled funnel plot of meta-analysis in overall cancer: allele comparing model.

increased risk of cancer, especially, in gastric cancer, pancreatic cancer, hepatocellular carcinoma, digestive system cancer and Asians subgroups. In the future, more large-scale and well-designed epidemiological studies are warranted to validate or refute these findings.

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Disclosure of conflict of interest

None.

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