Technology in Cancer Research & Treatment
Volume 20: 1-16

DOI: 10.1177/15330338211037813
journals.sagepub.com/home/tct
SAGE

PAI-1 Polymorphisms Have Significant Associations With Cancer Risk, Especially Feminine Cancer

Jiaxi Wang, MD[1,2,3,4,*], Yuanyuan Peng, MM[1,*], Hejia Guo, MBBS[5,*], and Cuiping Li, PhD[2,3,4,6]

Abstract

Background: The plasminogen activator inhibitor-1 (PAI-1) was found in many types of tumor cells, which involved in tumorigenesis. Some studies investigated the associations between PAI-1 polymorphisms and various cancers, but the results were inconsistent. So this study did a meta-analysis to assess the strength of relationship between PAI-1 and cancer. **Methods:** Articles that meet the requirements were searched from PubMed, EMBASE, MEDLINE, Scopus, CNKI, Wanfang and SinoMed electronic databases before June 17th 2021. Stata version 11.2 was performed to merge the odds ratios (ORs) values and calculate 95% confidence intervals (CIs). Stratified analyses were assessed on the basis of types of cancer, ethnicity and source of the control group. Heterogeneity and sensitivity analysis were tested, and publication bias was also estimated. A meta-regression analysis was applied to explore sources of heterogeneity. The false-positive report probabilities (FPRP) and the Bayesian False Discovery Probability (BFDP) test were used to assess the credibility of statistically significant associations. **Results:** Ultimately, in this study, 33 eligible reports were included with 9550 cases and 10431 controls for the rs1799889 polymorphism, 5 reports with 2705 cases and 3168 controls for the rs2227631 polymorphism, and 4 reports with 2799 cases and 4011 controls for the rs2227667 polymorphism. The ORs and 95% CIs showed a statistically significant relationship between rs1799889 4G>5G polymorphism and cancer risk, especially in feminine cancer. The term refers to cancers that occur in the female reproductive system, such as ovarian, breast, endometrial and cervical cancer. Moreover, there was no association observed for the PAI-1 promoter A>G polymorphism (rs2227631 and rs2227667). In further subgroup analyses of 4G>5G polymorphism (rs1799889), an increased susceptibility to cancer was observed in Caucasians group and some types of cancer groups. **Conclusions:** This article comes to a conclusion that the rs1799889 polymorphism might help to increase the risk of cancer; moreover, the susceptibility to feminine cancer is more evident.

Keywords

cancer, polymorphism, PAI-1, meta-analysis

Abbreviations

PAI-1, plasminogen activator inhibitor-1; Ors, odds ratios; Cis, confidence intervals; SNP, single nucleotide polymorphism.

Received: March 29, 2021; Revised: July 02, 2021; Accepted: July 14, 2021.

[1] Department of Periodontal and Oral Medicine, College and Hospital of Stomatology, Guangxi Medical University, Nanning, People's Republic of China
[2] Guangxi Key Laboratory of Oral and Maxillofacial Rehabilitation and Reconstruction, Nanning, People's Republic of China
[3] Guangxi Key Laboratory of Oral and Maxillofacial Surgery Disease Treatment, Nanning, People's Republic of China
[4] Guangxi Clinical Research Center for Craniofacial Deformity, Guangxi Health Commission Key Laboratory of Prevention and Treatment for Oral Infectious Diseases, College of Stomatology, Guangxi Medical University, Nanning, People's Republic of China
[5] Department of Oral and Maxillofacial Surgery, College and Hospital of Stomatology, Guangxi Medical University, Nanning, People's Republic of China
[6] Medical Scientific Research Center, College of Stomatology, Guangxi Medical University, Nanning, People's Republic of China
*Jiaxi Wang, Yuanyuan Peng, and Hejia Guo contributed equally to this work.

Corresponding Author:
Cuiping Li, PhD, Department of Experiment, the Affiliated Stomatology Hospital of Guangxi Medical University, Nanning 530021, People's Republic of China.
Email: gxcuiping@sina.com

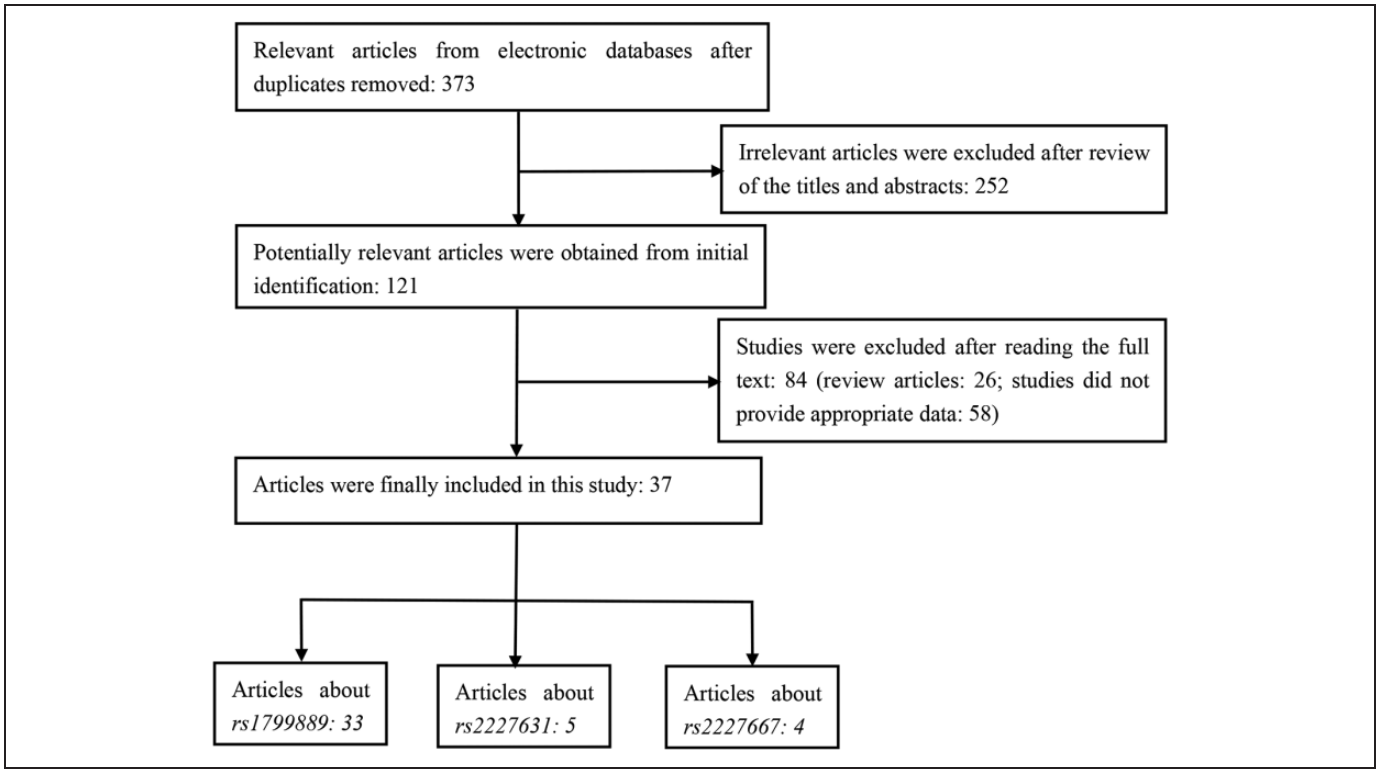

Figure 1. The whole flow diagram of filtering the available articles in this study.

Introduction

Cancer is a primarily public health issue and global problem with high mortality rates. Substantial and convincing evidences suggested that genetic factors were indispensable factors of the pathogenesis of cancer. The study of genetic variation has had an enormous impact on the belief within the last 30 or so years that could directly or indirectly link specific variants with specific traits or diseases. The commonest type of gene mutation is single nucleotide polymorphism (SNP) at the genomic level, accounting for more than 90% of all known polymorphisms. SNPs could be applied to detect alleles at polymorphic sites for indirectly or directly physiological correlation with traits or disease.[1] In other words, researchers have found that some sorts of cancers, such as ovarian, breast and lung, were associated with genetic polymorphism via SNPs test.

Plasminogen activator inhibitor type 1 (PAI-1) made a critical difference in tumor progression, involving in degradation of the basement membrane and tumor stroma.[2] PAI-1 could inhibit the expression of active plasmin which degraded the fibrin. Hence overexpression of PAI-1 might lead to fibrinolytic system dysfunction, thereby further increasing thrombosis risk.[3,4] Therefore, PAI-1 regulated the growth, invasion and angiogenesis of many types of cancer cell in a dose-dependent manner.[5,6] The level of PAI-1 expression had been found to be modulated by its own genetic polymorphism, of which the most relevant SNP was a single guanosine nucleotide insertion/deletion variation (4G>5G). The location of 4G allele of 4G>5G polymorphism was the promoter region −675 base pairs upstream, PAI-1 gene (rs1799889) could cause an increase in expression levels of PAI-1 in plasma, which suggested that PAI-1 gene (rs1799889) had an effect on the binding of nuclear proteins. This nuclear proteins participated in the regulation of PAI-1 gene transcription and conditioned a clear hypo-fibrinolytic state.[7] In addition, the single nucleotide polymorphism identified in the promoter region −844 G/A (rs2227631) was be investigated.[8] Up to now, the studies that have been published frequently focused on 3 variants of the PAI-1 gene including the rs1799889/rs2227631/rs2227667 polymorphisms.

In order to get a farther understanding of the PAI-1 gene, many case-control reports have explored the correlation between the rs1799889/rs2227631/rs2227667 polymorphisms and the risk of different types of cancers. Nevertheless, these reports also showed inconsistency findings. To address these issues, this meta-analysis was conducted to obtain a more precise verdict about the relationship between the rs1799889/rs2227631/rs2227667 polymorphisms and cancer risks.

Materials and Methods

Strategy for Retrieving Qualified Articles in the Database

The studies about the relation between rs1799889, rs2227631, or rs2227667 polymorphisms and cancer risks were identified and the databases used in this study were PubMed, EMBASE, MEDLINE, Scopus, CNKI, Wanfang and SinoMed electronic

databases. The searches identified the eligible publications using the following terms and keywords in the variety of ways: (1) "PAI-1"/"plasminogen activator inhibitor-1"/"SERPINE1"; (2) "polymorphism"/"geneotype"/"gene mutation"/"variant"/ "variation"; (3) "carcinoma"/"cancer"/ "tumor." The time cut-off point for this searching work was June 17th, 2021.

In order not to miss relevant important articles, we searched carefully and manually all qualified articles, review articles and other relevant studies and the search was repeated several times. Unpublished articles were not under discussion. We had registered our study with INPLASY. The registration number was INPLASY202160026, and the DOI number was 10.37766/inplasy2021.6.0026.

The Selection Criteria of Eligible Articles and Quality Assessment

The criteria of eligible articles: (1) evaluation of the link between at least one of these 3 polymorphisms (SERPINE1 rs1799889, rs2227631, rs2227667) and cancer risk; (2) published language: English, Chinese; (3) enough data to be available for odds ratios (OR) with the 95% confidence interval (95% CI) calculation; (4) study design: case-control; (5) If many studies from the same datum were available, only the studies with larger sample size or most recent studies were included in this study.

The studies were excluded according to the following criteria: (1) duplicate of previous published articles; (2) studies without essential data; (3) reviews, only abstracts, and studies with none of these 3 polymorphisms (SERPINE1 rs1799889, rs2227631, rs2227667).

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9]

The Newcastle-Ottawa scale (NOS) was proposed by Wells *et al* in the website (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm), which was used to assess the quality of eligible articles. The checklist of NOS had 3 parts: selection, comparability and exposure, as well as a score range of 0 to 9.

Data Extraction

Two independent researches (Jiaxi Wang, Yuanyuan Peng) carefully selected relevant studies separately according the inclusive criteria. Another researches (Cuiping Li, Hejia Guo) checked the extraction of original data. If any controversial issue remained, all researches reached a consensus after discussions. The data collected from each article included first author's last name, the published time of papers, ethnicity, country, the types of cancer, source of control and number of genotypes. Ethnicities were generally categorized as Caucasian and Asian. If some articles included more than one ethnic descent or had difficulty in distinguishing participants form original literature, the ethnicity in these kinds of articles was categorized as mixed ethnicity.

Data Calculation

Crude ORs and 95% CI were applied to calculate and analyze the relationship between rs1799889 polymorphisms and cancer risk in 4 models (homozygous model: 4G4G vs 5G5G; heterozygous model: 4G4G vs 4G5G; recessive model: 4G4G vs 5G4G+5G5G; dominant model: 4G4G+5G4G vs 5G5G). Subgroup analyses were calculated by ethnicity, source of controls and cancer types respectively. Crude ORs and 95% CI were applied to calculate and analyze the association between rs2227631/rs2227667 polymorphisms and the susceptibility to cancer in homozygous model (AA vs GG), heterozygous model (AA vs AG), recessive model (AA vs AG+GG) and dominant genetic model (AA+AG vs GG).

Heterogeneity was calculated and analyzed by using I^2 value and P value. I^2 statistic indicated the proportion of total variation which was caused by the variation between study and study. The random effects model was used when there were statistical differences found in heterogeneity ($P < 0.05$, $I^2 > 50\%$), or else the fixed effects model was conducted ($P > 0.05$, $I^2 < 50\%$). Publication bias was used to calculate statistically by the Egger's linear regression test. STATA version 11.2 (Stata Corp, College Station, TX, USA) counted all the results, using the P values of 2-sided ($P < 0.05$: statistical significance; $P \geq 0.05$: no statistical significance). Meta-regression analysis were applied to the predefined sources of heterogeneity on the base of year of population, and ethnicity. Sensitivity analyses were carried out to check the rationality of our meta-analysis results by eliminating studies that deviated from HWE. Sensitivity analysis was to exclude 1 study at a time and combined the remaining studies to detect whether there was any influence on the results, if the original synthetic results included at least 5 studies.

The false positive report probability (FPRP) was calculated to evaluate significance findings. We set the threshold for FPRP at 0.2 and specified a prior probability of 0.25, 0.1, 0.01, 0.001 and 0.0001 to detect that a odds ratio (OR) of 1.5 was associated with cancer risk in the study. The results were considered noteworthy only if the FPRP value is less than 0.2.[10]

Bayesian false discovery probability (BFDP) was estimated using Excel calculation spreadsheet to assess the credibility of statistically significant associations.[11] BFDP values below 0.8 were considered to be noteworthy.

Results

Study Characteristics

Totally, 373 possibly relevant articles were selected after duplicates were removed by searching online databases, according to the search criteria (Figure 1). A total of 252 irrelevant studies were deleted after reading the titles and abstracts of every single article in detail. A total of 121 potential reports were checked with the reference criteria from the mention above. After reading the full text, 84 articles were removed (58 articles: no sufficient data + 26 articles: review). No other articles were found from the references manually. A total of 37 articles

Table 1. The Main Characteristics of the Eligible Studies for Rs1799889, Rs2227631 and Rs2227667 Polymorphism.[a]

No.	Author	Year	Ethnicity	Country	Cancer type	Source of control	Sample size of case	Sample size of control	Ca4G/4G	Ca4G/5G	Ca5G/5G	Con4G/4G	Con4G/C5G	Con5G/5G	Genotyping method	HWE	NOS score
rs1799889																	
1	Türkmen	1997	Caucasian	German	Ovarian	NA	22	23	1	10	11	2	10	11	PCR-RFLP	Yes	6
2	Smolarz	1999	Caucasian	Poland	Breast	NA	37	53	15	14	8	11	23	19	Allele-specific PCR	Yes	7
3	Blasiak	2000	Caucasian	Poland	Breast	NA	100	106	31	40	29	21	48	37	PCR-SSCP	Yes	7
4	Loktionov	2003	Caucasian	UK	Colorectal	HB	206	355	60	94	52	85	187	83	PCR-SSCP	Yes	8
5	Bi	2004	Asian	China	Breast	PB	53	146	18	29	6	43	87	16	PCR-SSCP	Yes	8
6	Zhou	2005	Asian	China	Ovarian	HB	52	30	18	25	9	10	15	5	PCR-SSCP	Yes	8
7	Zhang	2005	Asian	China	Leukemia	NA	30	30	16	10	4	13	12	5	Allele-specific PCR	Yes	8
8	Sternlicht	2006	Caucasian	USA	Breast	PB	2539	1832	790	1229	520	550	896	386	Minisequencing	Yes	8
9	Försti	2007	Caucasian	German	Colorectal	PB	304	581	107	137	60	210	266	105	Taqman	Yes	9
10	Woo	2007	Asian	Korea	Colorectal	NA	185	304	67	84	34	108	137	59	PCR-RFLP	Yes	8
11	Minisini	2007	Caucasian	Italy	Breast	NA	193	142	56	85	52	39	68	35	Allele-specific PCR	Yes	6
12	Lei	2008	Caucasian	German	Breast	PB	956	933	322	482	152	326	453	164	Taqman	Yes	9
13	Bentov	2009	Mixed	Canada	Ovarian	HB	772	889	226	372	174	257	440	192	MALDI-TOF	Yes	8
14	Palmirotta	2009	Caucasian	Italy	Breast	NA	99	50	26	43	30	10	29	11	Sequencing	Yes	8
15	Weng	2010	Asian	China	Hepatocellular	NA	102	344	27	58	17	87	181	76	PCR-RFLP	Yes	8
16	Su	2011	Asian	China	Endometrial	HB	134	302	49	67	18	77	161	64	PCR-RFLP	Yes	8
17	Vossen	2011	Caucasian	Netherlands	Colorectal	PB	1731	1799	523	816	353	523	929	347	Taqman	Yes	8
18	Weng	2011	Asian	China	Oral	HB	253	344	64	136	53	87	181	76	PCR-RFLP	Yes	8
19	Onur	2012	Caucasian	Turkey	Mixed	NA	28	50	6	10	12	28	38	34	2 parallel PCR	Yes	8
20	Tee	2012	Asian	China	Cervical	HB	75	336	53	59	24	102	169	65	PCR-RFLP	Yes	7
21	Gilabert-Estelles	2012	Spain	Caucasian	Endometrial	PB	212	211	51	118	43	35	111	65	Real-time PCR	Yes	9
22	Divella	2012	Caucasian	Italy	Hepatic	PB	75	50	27	20	28	8	15	27	Allele-specific PCR	Yes	9
23	Vylliotis	2013	Caucasian	Greek and German	Oral	NA	104	106	45	47	12	31	43	32	PCR-RFLP	Yes	8
24	Ramos-Flores	2013	Caucasian	Mexico	Cervical	NA	100	100	0	45	55	3	30	67	PCR-SSCP	Yes	7
25	Ozen	2013	Caucasian	Turkey	Breast	NA	51	106	8	30	13	10	62	34	StripAssay	Yes	8
26	Bayramoglu	2014	Caucasian	Turkey	Lung	HB	156	132	49	48	59	28	22	82	Allele-specific PCR	Yes	7
27	Mitrovic	2014	Caucasian	Serbia	Leukemia	PB	34	126	10	15	9	44	58	24	PCR-RFLP	Yes	8
28	Pooyan	2015	Caucasian	Iran	Glioblastoma	HB	71	140	21	30	20	13	84	43	ARMS-PCR	Yes	7

(continued)

Table 1. (continued)

No.	Author	Year	Ethnicity	Country	Cancer type	Source of control	Sample size of case	Sample size of control	Ca4G/ 4G	Ca4G/ 5G	Ca5G/ 5G	Con4G/ 4G	Con4G/ C5G	Con5G/ 5G	Genotyping method	HWE	NOS score
29	Edel	2016	Caucasian	Egypt	Hepatic	NA	49	105	8	24	17	2	49	36	Allele-specific PCR	Yes	7
30	Yildirim	2017	Caucasian	Turkey	Endometrial	NA	82	76	22	51	9	11	43	22	PCR-RFLP	Yes	8
31	Zhang	2018	Asian	China	Nasopharyngeal	HB	86	35	28	44	14	12	17	6	PCR-RFLP	Yes	8
32	Oh	2020	Asian	Korea	Colorectal	PB	459	416	171	206	82	180	180	56	PCR-RFLP	Yes	9
33	Pouladi	2021	Caucasian	Iranian-Azeri	Breast	NA	200	179	22	141	37	20	127	32	ARMS-PCR	Yes	7
rs2227631																	
1	Bentov	2009	Mixed	Canada	Ovarian	HB	766	888	260	362	144	315	425	148	MALDI-TOF	Yes	8
2	Ju	2010	Asian	Korea	Gastric	NA	249	406	20	122	109	58	177	166	MALDI-TOF	Yes	8
3	Pooyan	2015	Caucasian	Iran	Glioblastoma	HB	71	140	14	33	24	5	81	54	ARMS-PCR	Yes	7
4	Chen	2016	Asian	China	Breast	NA	1160	1318	194	519	447	224	607	487	TaqMan	Yes	8
5	Oh	2020	Asian	Korea	Colorectal	PB	459	416	75	230	154	81	199	136	PCR-RFLP	Yes	9
rs2227667																	
1	Ju	2010	Asian	Korea	Gastric	NA	249	406	57	141	51	142	190	74	MALDI-TOF	Yes	8
2	Purdue	2011	Caucasian	USA	myeloma	PB	103	475	76	26	26	255	198	20	GoldenGate platform	Yes	9
3	Martino	2014	Caucasian	Mixed	myeloma	PB	1287	1812	762	457	68	1080	623	109	TaqMan and KASPar	Yes	9
4	Chen	2016	Asian	China	Breast	NA	1160	1318	216	551	393	269	618	431	TaqMan	Yes	8

Abbreviations: NA, not available; PB, population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale.
[a]Mixed ethnicity: those studies with more than one ethnic group or those difficult to separate participants.

Table 2. Stratified Analyses of the Rs1799889 Polymorphism on Cancer Risk.[a]

Comparative model	No.	Z	*P*	OR (95% CI)	Heterogeneity			Begg's test		Egger's test		FPRP *P*-value[b]	FPRP statistical power[c]	FPRP prior probability					BFDP prior probability		
					Heterogeneity chi-squared	*P*	I^2	Z		t				0.25	0.10	0.01	0.001	0.0001	0.01	0.001	0.000001
4G4G/5G5G																					
Overall	33	3.22	0.001	1.297(1.107-1.519)	75.13	0	57.4%	1.29	0.198	2.6	0.016	0.001	0.964	**0.004**	**0.012**	**0.114**	0.565	0.929	0.809	0.977	1.000
Ethnicity																					
Caucasian	22	3.31	0.001	1.435(1.159-1.778)	60.38	0	65.20%	0.73	0.463	2.4	0.027	0.001	0.657	**0.004**	**0.013**	**0.126**	0.593	0.936	**0.730**	0.965	1.000
Asian	10	0.78	0.435	1.082(0.887-1.320)	13.09	0.159	31.20%	0.36	0.721	1.1	0.289	0.437	0.999	0.568	0.797	0.977	0.998	1.000	0.998	1.000	1.000
Source of control																					
HB	9	2.35	0.019	1.429(1.061-1.925)	18.24	0.019	56.10%	1.36	0.175	1.6	0.146	0.019	0.625	**0.083**	0.214	0.749	0.968	0.997	0.967	0.997	1.000
PB	9	0.46	0.644	1.048(0.859-1.278)	19.45	0.013	58.90%	0.31	0.754	0.6	0.603	0.643	1.000	0.659	0.853	0.985	0.998	1.000	0.998	1.000	1.000
Cancer types																					
Ovarian	3	0.27	0.789	0.965(0.74-1.257)	0.26	0.878	0.00%					0.792	0.997	0.704	0.877	0.987	0.999	1.000	0.998	1.000	1.000
Breast	9	1.46	0.145	1.102(0.967-1.257)	7.35	0.499	0.00%					0.148	1.000	0.308	0.571	0.936	0.993	0.999	0.997	1.000	1.000
Colorectal	5	0.89	0.371	0.936(0.811-1.081)	4.4	0.354	9.20%					0.368	1.000	0.525	0.768	0.973	0.997	1.000	0.998	1.000	1.000
Oral	2	1.02	0.308	1.937(0.543-6.907)	7.41	0.006	86.50%					0.308	0.347	0.727	0.889	0.989	0.999	1.000	0.991	0.999	1.000
Hepatocellular	3	2.11	0.035	2.72(1.076-6.88)	4.97	0.084	59.70%					0.035	0.104	0.498	0.749	0.970	0.997	1.000	0.977	0.998	1.000
Endometrial	3	4.51	0	2.487(1.674-3.696)	1.81	0.404	0.00%					0.000	0.006	**0.003**	**0.009**	**0.095**	0.515	0.914	**0.035**	**0.269**	0.974
Cervical	2	0.93	0.353	1.306(0.743-2.295)	1.82	0.177	45.10%					0.353	0.685	0.607	0.823	0.981	0.998	1.000	0.994	0.999	1.000
Leukemia	2	0.46	0.648	0.822(0.353-1.91)	1	0.316	0.4					0.649	0.687	0.739	0.895	0.989	0.999	1.000	0.993	0.999	1.000
4G4G/4G5G																					
Overall	33	2.68	0.007	1.095(1.025-1.170)	46.15	0.05	30.70%	1.41	0.159	2.2	0.038	0.007	1.000	**0.021**	**0.061**	0.418	0.879	0.986	0.978	0.998	1.000
Ethnicity																					
Caucasian	22	2.68	0.007	1.113(1.029-1.203)	37.13	0.016	43.40%	1.02	0.31	2	0.06	0.007	1.000	**0.020**	**0.059**	0.408	0.874	0.986	0.974	0.997	1.000
Asian	10	0.69	0.488	1.055(0.906-1.229)	8.46	0.488	0.00%	1.25	0.21	1.2	0.27	0.492	1.000	0.596	0.816	0.980	0.998	1.000	0.998	1.000	1.000
Source of control																					
HB	9	1.92	0.055	1.270(0.995-1.620)	17.25	0.028	53.60%	1.15	0.251	1	0.356	0.054	0.910	**0.152**	0.349	0.855	0.983	0.998	0.987	0.999	1.000
PB	9	0.99	0.321	1.042(0.960-1.131)	9.43	0.307	15.20%	0.52	0.602	0.6	0.562	0.325	1.000	0.494	0.745	0.970	0.997	1.000	0.999	1.000	1.000
Cancer types																					
Ovarian	3	0.32	0.75	1.036(0.832-1.291)	0.32	0.852	0.00%					0.753	1.000	0.693	0.871	0.987	0.999	1.000	0.998	1.000	1.000
Breast	9	0.98	0.329	1.054(0.949-1.171)	8.23	0.412	2.80%					0.327	1.000	0.496	0.747	0.970	0.997	1.000	0.998	1.000	1.000
Colorectal	5	1.17	0.243	1.070(0.955-1.200)	5.56	0.234	28.10%					0.247	1.000	0.426	0.690	0.961	0.996	1.000	0.998	1.000	1.000
Oral	2	0.39	0.693	1.069 (0.768-1.488)	0.67	0.413	0.00%					0.693	0.978	0.680	0.864	0.986	0.999	1.000	0.997	1.000	1.000
Hepatocellular	3	1.38	0.166	2.224 (0.717-6.896)	7.68	0.022	74%					0.166	0.248	0.668	0.858	0.985	0.999	1.000	0.989	0.999	1.000
Endometrial	3	2.48	0.013	1.486(1.086-2.033)	0.2	0.903	0.00%					0.013	0.523	**0.071**	**0.186**	0.715	0.962	0.996	0.955	0.995	1.000
Cervical	2	1.51	0.132	1.403(0.903-2.179)	3.15	0.076	68.20%					0.132	0.617	0.390	0.658	0.955	0.995	1.000	0.990	0.999	1.000
Leukemia	2	0.21	0.836	1.076(0.539-2.146)	0.51	0.476	0					0.835	0.827	0.752	0.901	0.990	0.999	1.000	0.995	0.999	1.000
4G4G/4G5G+5G5G																					
Overall	33	3.12	0.002	1.104(1.038-1.176)	60.98	0.002	47.50%	1.66	0.097	2.8	0.009	0.002	1.000	**0.006**	**0.019**	**0.175**	0.682	0.955	0.940	0.994	1.000
Ethnicity																					
Caucasian	22	3.4	0.001	1.302(1.118-1.516)	47.34	0.001	55.60%	1.18	0.236	2.7	0.016	0.001	0.966	**0.002**	**0.006**	**0.065**	0.412	0.875	**0.714**	0.962	1.000
Asian	10	0.75	0.45	1.057(0.916-1.220)	12.49	0.187	27.90%	1.25	0.21	1.3	0.231	0.448	1.000	0.573	0.801	0.978	0.998	1.000	0.998	1.000	1.000
Source of control																					
HB	9	2.52	0.012	1.352(1.07-1.708)	18.46	0.018	56.70%	1.36	0.175	1.7	0.127	0.011	0.808	**0.041**	**0.113**	0.584	0.934	0.993	0.957	0.996	1.000
PB	9	0.54	0.588	1.036(0.912-1.176)	14.81	0.063	46.00%	0.73	0.466	0.7	0.507	0.584	1.000	0.637	0.840	0.983	0.998	1.000	0.999	1.000	1.000

(continued)

Table 2. (continued)

Comparative model	No.	Z	*P*	OR (95% CI)	Heterogeneity			Begg's test		Egger's test		FPRP *P*-value[b]	FPRP statistical power[c]	FPRP prior probability					BFDP prior probability		
					Heterogeneity chi-squared	*P*	I^2	Z		t				0.25	0.10	0.01	0.001	0.0001	0.01	0.001	0.000001
Cancer types																					
Ovarian	3	0.14	0.889	1.015(0.825-1.247)	0.32	0.851	0.00%					0.887	1.000	0.727	0.889	0.989	0.999	1.000	0.998	1.000	1.000
Breast	9	1.24	0.215	1.065(0.964-1.176)	9.13	0.332	12.30%					0.213	1.000	0.390	0.657	0.955	0.995	1.000	0.998	1.000	1.000
Colorectal	5	0.47	0.639	1.026(0.922-1.142)	6.38	0.172	37.30%					0.639	1.000	0.657	0.852	0.984	0.998	1.000	0.999	1.000	1.000
Oral	2	0.88	0.379	1.306(0.72-2.368)	3.1	0.078	67.70%					0.379	0.676	0.627	0.835	0.982	0.998	1.000	0.994	0.999	1.000
Hepatocellular	3	1.61	0.106	2.444(0.826-7.232)	8.42	0.015	76.30%					0.106	0.189	0.628	0.835	0.982	0.998	1.000	0.986	0.999	1.000
Endometrial	3	3.5	0	1.707(1.265-2.304)	0.42	0.81	0.00%					0.000	0.199	**0.007**	**0.021**	**0.191**	0.704	0.960	**0.561**	0.928	0.999
Cervical	2	0.3	0.768	0.728(0.088-6.01)	2.37	0.124	57.70%					0.768	0.533	0.812	0.928	0.993	0.999	1.000	0.991	0.999	1.000
Leukemia	2	0.01	0.994	1.003(0.533-1.884)	0.96	0.327	0					0.993	0.895	0.769	0.909	0.991	0.999	1.000	0.995	1.000	1.000
4G4G+4G5G/5G5G																					
Overall	33	1.97	0.049	1.072(1.000-1.150)	62.76	0.001	49.00%	1.07	2.85	2.2	0.035	0.052	1.000	**0.136**	0.320	0.838	0.981	0.998	0.996	1.000	1.000
Ethnicity																					
Caucasian	22	2.42	0.016	1.217(1.038-1.427)	53.13	0	60.50%	0.73	0.463	2	0.057	0.016	0.995	**0.045**	**0.124**	0.608	0.940	0.994	0.975	0.997	1.000
Asian	10	0.61	0.541	1.057(0.886-1.261)	8.39	0.459	0.00%	0.36	0.721	0.9	0.395	0.538	1.000	0.617	0.829	0.982	0.998	1.000	0.998	1.000	1.000
Source of control																					
HB	9	1.48	0.138	1.212(0.940-1.562)	18.5	0.018	56.70%	0.73	0.466	0.9	0.381	0.137	0.950	0.303	0.566	0.935	0.993	0.999	0.994	0.999	1.000
PB	9	0.23	0.82	1.018(0.871-1.191)	16.2	0.04	50.60%	0.1	0.917	0.4	0.679	0.824	1.000	0.712	0.881	0.988	0.999	1.000	0.999	1.000	1.000
Cancer types																					
Ovarian	3	0.49	0.626	0.946(0.756-1.183)	0	0.998	0.00%					0.626	0.999	0.653	0.849	0.984	0.998	1.000	0.998	1.000	1.000
Breast	9	0.94	0.347	1.055(0.943-1.181)	5.1	0.747	0.00%					0.352	1.000	0.514	0.760	0.972	0.997	1.000	0.998	1.000	1.000
Colorectal	5	1.8	0.072	0.891(0.785-1.010)	1.99	0.737	0.00%					0.071	1.000	**0.176**	0.390	0.876	0.986	0.999	0.994	0.999	1.000
Oral	2	1.05	0.295	1.804(0.597-5.445)	7.11	0.008	85.90%					0.295	0.372	0.704	0.877	0.987	0.999	1.000	0.991	0.999	1.000
Hepatocellular	3	2.16	0.031	1.527(1.039-2.243)	0.68	0.713	0.00%					0.031	0.464	0.167	0.375	0.869	0.985	0.999	0.974	0.997	1.000
Endometrial	3	3.92	0	1.912(1.383-2.643)	1.85	0.396	0.00%					0.000	0.071	**0.004**	**0.011**	**0.109**	0.551	0.925	**0.227**	**0.748**	0.997
Cervical	2	1.48	0.139	1.336(0.910-1.962)	1	0.316	0.40%					0.140	0.723	0.367	0.635	0.950	0.995	0.999	0.991	0.999	1.000
Leukemia	2	0.58	0.559	0.799(0.376-1.697)	0.65	0.421	0					0.559	0.681	0.711	0.881	0.988	0.999	1.000	0.994	0.999	0.999

Abbreviations: OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based; FPRP, false positive report probability; BFDP, Bayesian False Discovery Probability.

[a]The results in bold represented there was statistically significant noteworthiness at 0.2 level by FPRP or 0.8 level by BFDP calculations.

[b]Chi-square test was used to calculate the genotype and haplotype frequency distributions.

[c]Statistical power was the power to detect an odds ratio of 1.5 for the homozygotes with the rare genetic variant and 1 for the heterozygotes and for the homozygote with the common variant.

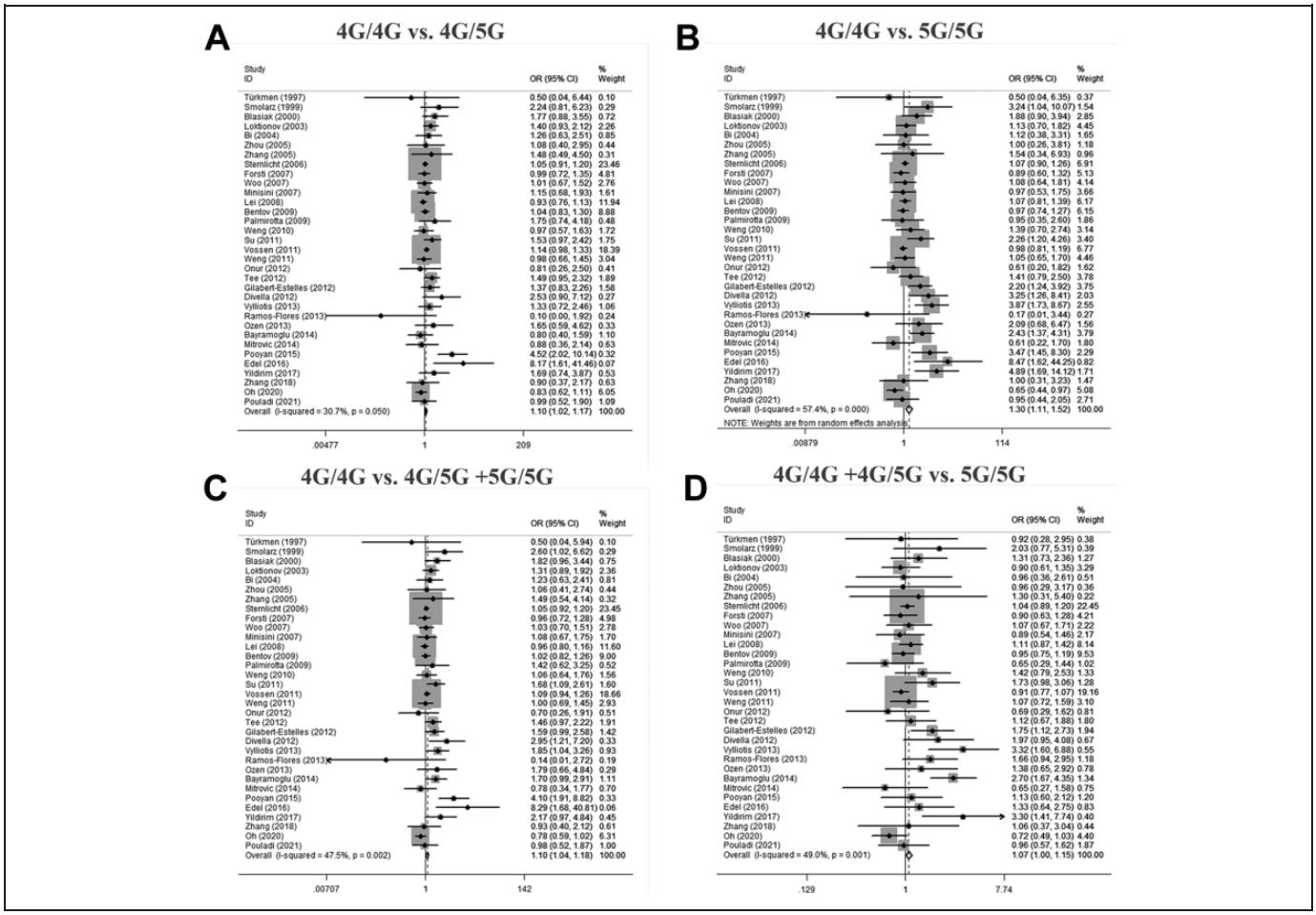

Figure 2. Forest plot of the statistical correlation between rs1799889 polymorphism and cancer susceptibility in all models (A: 4G4G vs 4G5G; B: 4G4G vs 5G5G; C: 4G4G vs 4G5G + 5G5G; D: 4G4G + 4G5G vs 5G5G). Data were pooled odds ratios (OR) with 95% confidence intervals (CI) determined using random-effects models or fixed-effects models according to I^2 values.

were identified in this article, which included 33 articles with 9550 cases and 10431 controls samples for the rs1799889 polymorphism,[8,12-43] 5 articles with 2705 cases and 3168 controls samples for the rs2227631 polymorphism[23,38,41,44,45] and 4 articles with 2799 cases and 4011 controls samples for the rs2227667 polymorphism.[44-47]

Concerning rs1799889 polymorphism, among the 33 case-control studies, there were 9 studies on breast cancer, 5 studies on colorectal cancer, 3 studies on ovarian cancer, 3 studies on endometrial cancer, 3 studies on hepatocellular cancer, 2 studies on oral cancer, 2 studies on leukemia cancer and 6 studies on other cancers (cervical cancer, lung cancer, glioblastoma, nasopharyngeal cancer); there were 9 hospital-based studies and 9 population-based studies; there were 22 studies for Caucasian, 10 studies for Asian and 1 study for mixed ethnicity. Concerning rs2227631 polymorphism, among the 5 case-control studies, there were one each studies consisted of the studies on ovarian cancer, breast cancer, gastric cancer, colorectal cancer and glioblastoma. Concerning ethnicity, 3 studies were subjects of Asian descent, 1 study was subjects of Caucasian descent and 1 study was a mixed population. Concerning rs2227667 polymorphism, among the 4 case-control studies, there were 2 studies on myeloma, one each studies on breast cancer and gastric cancer. Concerning ethnicity, there were 2 studies for Caucasian and 2 studies for Asian. The main characteristics of the eligible studies for rs1799889, rs2227631 and rs2227667 polymorphism were showed respectively in Table 1.

The NOS score of eligible articles was between 6 to 9, which indicated that the quality of included literatures were relatively high. Detailed scores were summarized in Table 1.

Quantitative Synthesis

Table 2 showed the overall OR with its 95% CI regarding the relationship between SERPINE1 rs1799889 polymorphism and cancer risk. When 33 studies were analyzed in all models,

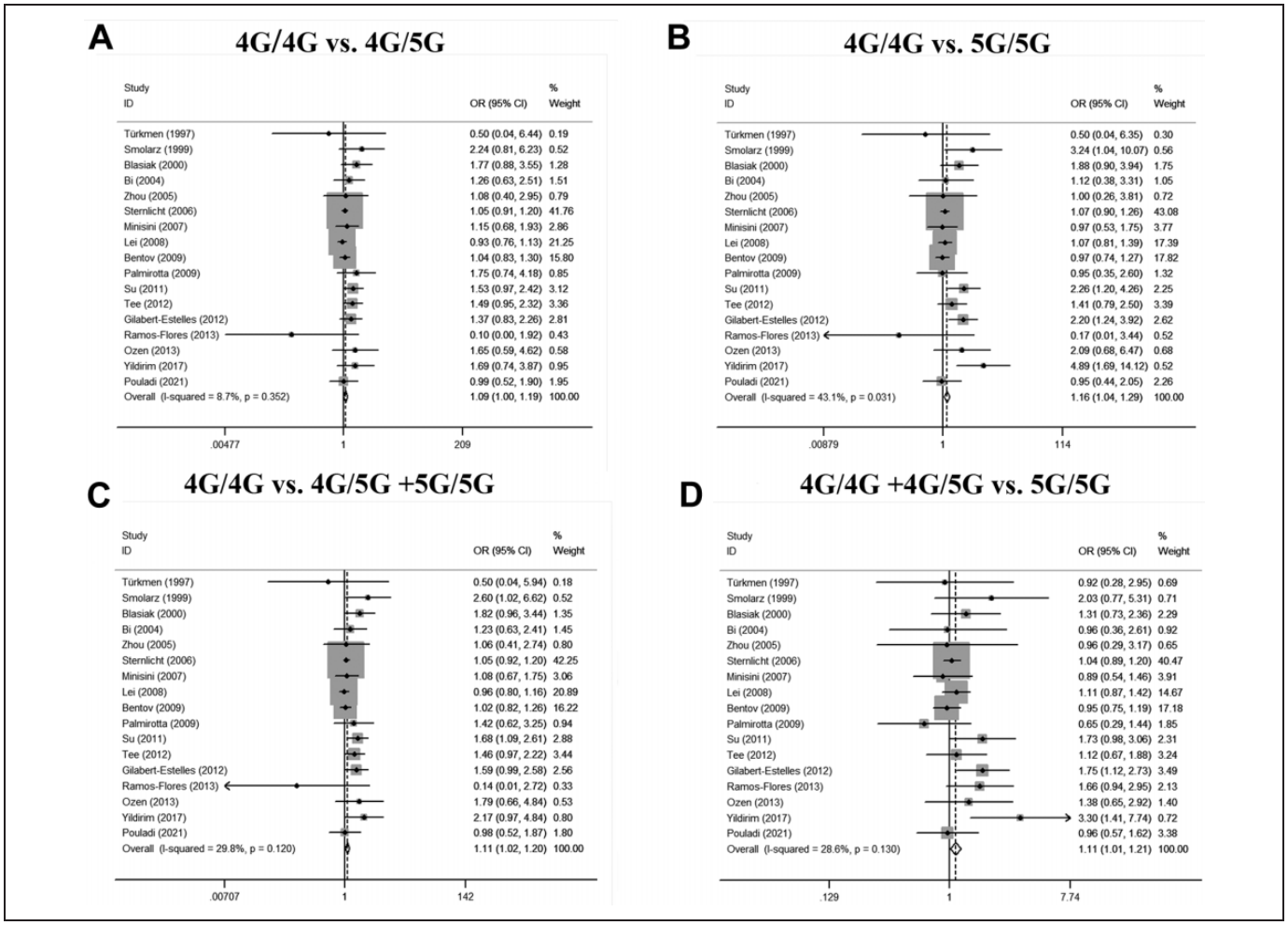

Figure 3. Forest plot of the statistical correlation between rs1799889 polymorphism and the susceptibility of feminine cancer in all models (A: 4G4G vs 4G5G; B: 4G4G vs 5G5G; C: 4G4G vs 4G5G + 5G5G; D: 4G4G + 4G5G vs 5G5G). Data were pooled odds ratios (OR) with 95% confidence intervals (CI) determined using random-effects models or fixed-effects models according to I^2 values.

the rs1799889 polymorphism statistically increased cancer susceptibility (4G4G vs 5G5G: OR (95%CI) = 1.297(1.107-1.519), $P = 0.001$; 4G4G vs 4G5G, OR (95%CI) = 1.095(1.025-1.170), $P = 0.007$; 4G4G vs 4G5G+5G5G, OR (95%CI) = 1.104 (1.038-1.176), $P = 0.002$; 4G4G+4G5G vs 5G5G, OR (95%CI) = 1.072(1.000-1.150), $P = 0.049$, (Figure 2 and Table 2). There were statistically increased risks among Caucasian populations in 4 models when conducting a stratified analysis based on ethnicity (4G4G vs 5G5G: OR (95%CI) = 1.435(1.159-1.778), $P = 0.001$; 4G4G vs 4G5G, OR (95%CI) = 1.113(1.029-1.203), $P = 0.007$; 4G4G vs 4G5G+5G5G, OR (95%CI) = 1.302(1.118-1.516), $P = 0.001$;4G4G+4G5G vs 5G5G, OR (95%CI) = 1.217(1.038-1.427), $P = 0.016$, Table 2). However, the increased risk was not found in all models of Asian populations. Moreover, there were statistical significances in some comparison models for hospital-based groups (4G4G vs 5G5G: OR (95%CI) = 1.429(1.061-1.925), $P = 0.019$; 4G4G vs 4G5G+5G5G, OR (95%CI) = 1.352(1.07-1.708), $P = 0.012$, Table 2). However, the increased risk was not found in all models of population-based groups.

The increased susceptibility to feminine cancer were observed (4G4G vs 5G5G: OR (95%CI) = 1.157(1.036-1.291), $P = 0.009$; 4G4G vs 4G5G+5G5G, OR (95%CI) = 1.107(1.018-1.204), $P = 0.017$; and 4G4G+4G5G vs 5G5G, OR (95%CI) = 1.106(1.008-1.214), $P = 0.033$, (shown in Figure 3 and Table 3). Feminine cancer is specific to women, including ovarian, breast, endometrial and cervical cancer in this study. The term refers to cancers that occur in the female reproductive system. The results of the stratified analysis based on ethnicity showed that the increased risk was detected among Asian populations in 3 models (4G4G vs 5G5G: OR (95%CI) = 1.586(1.087-2.314), $P = 0.017$; 4G4G vs 4G5G, OR (95%CI) = 1.426(1.08-1.884), $P = 0.012$; and 4G4G vs 4G5G+5G5G, OR (95%CI) = 1.462(1.123-1.903), $P = 0.005$, shown in Table 3). On the contrary, the increased risk was detected among Caucasians in 2 models (4G4G vs 5G5G: OR (95%CI) = 1.159(1.020-1.315), $P = 0.023$; and 4G4G+4G5G vs

Table 3. Stratified Analyses of the rs1799889 Polymorphism on Feminine Cancer Risk.[a]

Comparative model	No.	Z	*P*	OR (95% CI)	Heterogeneity chi-squared	Heterogeneity *P*	Heterogeneity I^2	Begg's test Z	Begg's test	Egger's test t	Egger's test	FPRP *P*-value[b]	FPRP statistical power[c]	FPRP prior probability 0.25	0.1	0.01	0.001	0.0001	BFDP prior probability 0.01	0.001	0.000001
4G4G/5G5G																					
Overall	17	2.60	0.009	1.157(1.036-1.291)	28.12	0.031	43.10%	0.37	0.711	1.62	0.126	0.009	1.000	**0.027**	**0.076**	0.474	0.901	0.989	0.972	0.997	1.000
Ethnicity																					
Caucasian	12	2.27	0.023	1.159(1.020-1.315)	21.72	0.027	49.30%					0.022	1.000	**0.062**	**0.165**	0.685	0.956	0.995	0.985	0.998	1.000
Asian	4	2.39	0.017	1.586(1.087-2.314)	2.23	0.526	0%					0.017	0.386	**0.115**	0.280	0.811	0.977	0.998	0.959	0.996	1.000
Source of control																					
HB	4	0.25	0.212	1.311(0.857-2.004)	6.4	0.094	53.10%					0.211	0.733	0.463	0.722	0.966	0.997	1.000	0.993	0.999	1.000
PB	4	1.52	0.129	1.113(0.969-1.279)	5.71	0.127	47.50%					0.131	1.000	0.282	0.541	0.929	0.992	0.999	0.996	1.000	1.000
4G4G/4G5G																					
Overall	17	1.92	0.054	1.091(0.998-1.192)	17.53	0.352	8.70%	0.12	0.902	1.83	0.087	0.054	1.000	0.139	0.326	0.842	0.982	0.998	0.995	0.999	1.000
Ethnicity																					
Caucasian	12	1.16	0.247	1.063(0.959-1.178)	13.02	0.292	15.50%					0.244	1.000	0.422	0.687	0.960	0.996	1.000	0.998	1.000	1.000
Asian	4	2.50	0.012	1.426(1.08-1.884)	0.55	0.908	0.00%					0.013	0.639	**0.055**	**0.150**	0.660	0.951	0.995	0.956	0.995	1.000
Source of control																					
HB	4	1.73	0.084	1.173(0.979-1.406)	3.5	0.32	14%					0.084	0.996	0.203	0.432	0.893	0.988	0.999	0.993	0.999	1.000
PB	4	0.49	0.624	1.028(0.921-1.147)	2.65	0.45	0.00%					0.621	1.000	0.651	0.848	0.984	0.998	1.000	0.999	1.000	1.000
4G4G/4G5G+5G5G																					
Overall	17	2.38	0.017	1.107(1.018-1.204)	22.78	0.12	29.80%	0.37	0.711	2	0.063	0.018	1.000	**0.050**	**0.137**	0.637	0.946	0.994	0.988	0.999	1.000
Ethnicity																					
Caucasian	12	1.66	0.096	1.086(0.985-1.197)	16.64	0.119	33.90%					0.097	1.000	0.225	0.465	0.905	0.990	0.999	0.997	1.000	1.000
Asian	4	2.82	0.005	1.462(1.123-1.903)	1.1	0.778	0.00%					0.005	0.576	**0.024**	**0.069**	0.449	0.892	0.988	0.907	0.990	1.000
Source of control																					
HB	4	1.78	0.075	1.168(0.984-1.385)	5.5	0.139	45.40%					0.074	0.998	**0.182**	0.400	0.880	0.987	0.999	0.993	0.999	1.000
PB	4	0.90	0.368	1.049(0.946-1.163)	3.94	0.268	23.90%					0.074	0.998	**0.182**	0.400	0.880	0.987	0.999	0.999	1.000	1.000
4G4G+4G5G/5G5G																					
Overall	17	2.14	0.033	1.106(1.008-1.214)	22.42	0.13	28.60%	0.7	0.484	1.65	0.12	0.034	1.000	**0.093**	0.235	0.771	0.971	0.997	0.992	0.999	1.000
Ethnicity																					
Caucasian	12	2.19	0.028	1.126(1.013-1.252)	18.09	0.08	39.20%					0.028	1.000	**0.078**	0.203	0.737	0.966	0.996	0.990	0.999	1.000
Asian	4	1.44	0.15	1.284(0.913-1.804)	1.89	0.595	0%					0.150	0.815	0.355	0.623	0.948	0.995	0.999	0.992	0.999	1.000
Source of control																					
HB	4	0.48	0.632	1.049(0.863-1.274)	3.83	0.28	21.70%					0.629	1.000	0.654	0.850	0.984	0.998	1.000	0.998	1.000	1.000
PB	4	1.5	0.135	1.096(0.972-1.236)	4.88	0.18	38.60%					0.135	1.000	0.288	0.549	0.930	0.993	0.999	0.997	1.000	1.000

Abbreviations: OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based; FPRP, false positive report probability; BFDP, Bayesian False Discovery Probability.

[a]The results in bold represented there was statistically significant noteworthiness at 0.2 level by FPRP or 0.8 level by BFDP calculations.

[b]Chi-square test was used to calculate the genotype and haplotype frequency distributions.

[c]Statistical power was the power to detect an odds ratio of 1.5 for the homozygotes with the rare genetic variant and 1 for the heterozygotes and for the homozygote with the common variant.

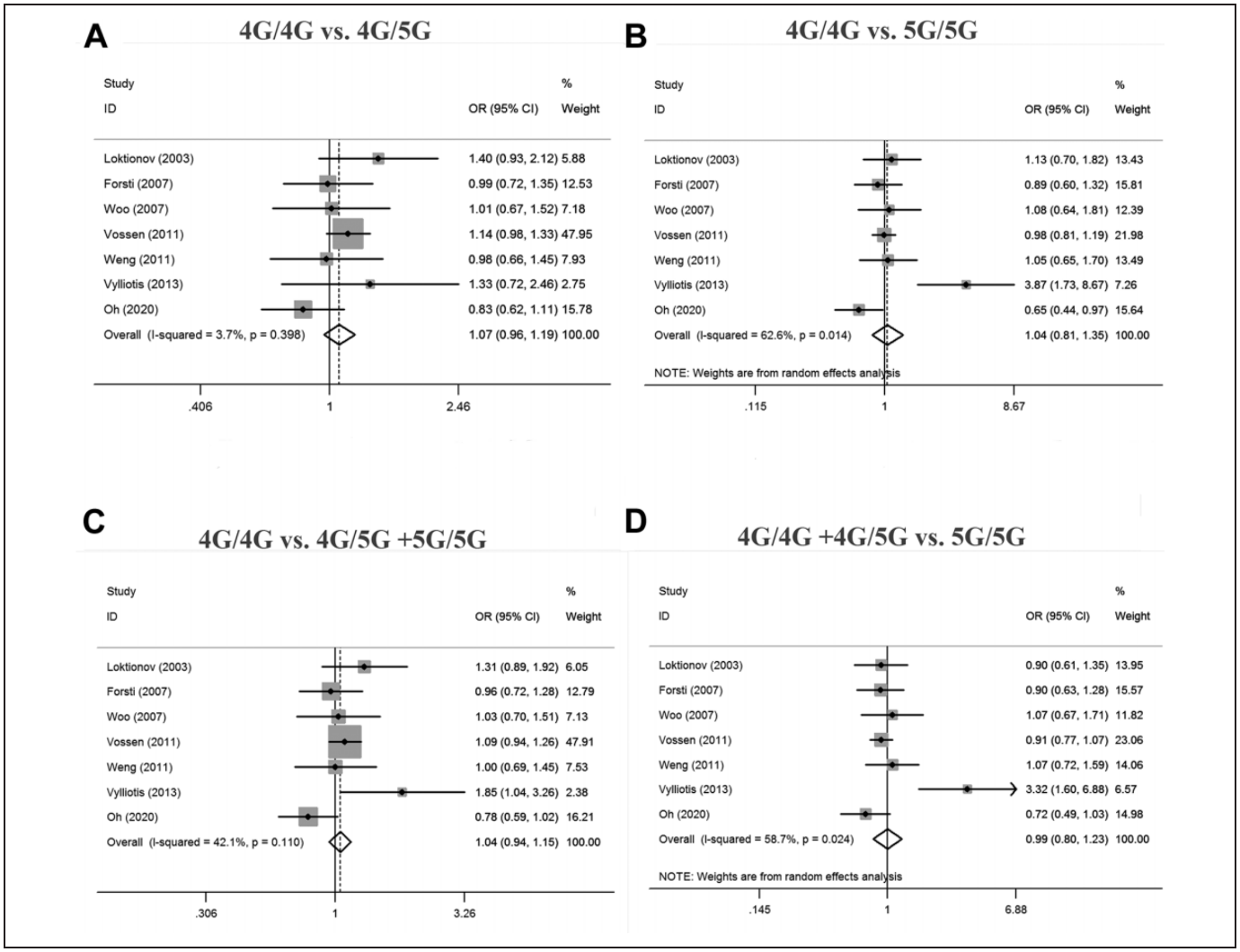

Figure 4. Forest plot of the correlation between rs1799889 polymorphism and the susceptibility of masticatory and gastrointestinal cancer in all models (A: 4G4G vs 4G5G; B: 4G4G vs 5G5G; C: 4G4G vs 4G5G + 5G5G; D: 4G4G + 4G5G vs 5G5G). Data were pooled odds ratios (OR) with 95% confidence intervals (CI) determined using random-effects models or fixed-effects models according to I^2 values.

5G5G, OR (95%CI) = 1.126(1.013-1.252), $P = 0.028$, shown in Table 3). However, the increased risk was not found in all models of hospital-based groups and population-based groups.

The increased or reduced susceptibility to masticatory and gastrointestinal cancer were not observed (shown in Figure 4 and Table 4). The increased risk was detected among Caucasian populations (4G4G vs 4G5G: OR (95%CI) = 1.142(1.005-1.297), $P = 0.042$, shown in Table 4). On the contrary, moreover, these results were similar among Asians, hospital-based groups and population-based groups.

Table 5 showed the overall OR with its 95% CI regarding the relationship between SERPINE1 rs2227631 polymorphism and cancer risk. No association between the rs2227631 polymorphism and cancer risk was detected (AA vs GG: OR (95%CI) = 0.925(0.65-1.316), $P = 0.665$; AA vs AG: OR (95%CI) = 0.975(0.686-1.386), $P = 0.888$; AA vs AG+GG: OR (95%CI) = 0.956(0.686-1.332), $P = 0.789$; and AA+AG vs GG: OR (95%CI) = 0.932(0.832-1.043), $P = 0.220$).

Table 5 showed the overall OR with its 95% CI regarding the SERPINE1 rs22276367 polymorphism and cancer risk. The results showed that no association between the rs2227667 polymorphism and cancer risk was detected (AA vs GG: OR (95%CI) = 0.649(0.393-1.071), $P = 0.091$; AA vs AG: OR (95%CI) = 0.980(0.687-1.398), $P = 0.911$; AA vs AG+GG: OR (95%CI) = 0.889(0.701-1.128), $P = 0.333$; and AA+AG vs GG: OR (95%CI) = 0.687(0.409-1.155), $P = 0.157$).

Publication Bias

Begg's test and Egger's test were used to assess about possible publication bias. According to the SERPINE1 rs1799889

Table 4. Stratified Analyses of the Rs1799889 Polymorphism on Masticatory and Gastrointestinal Cancer Risk.[a]

						Heterogeneity								FPRP prior probability					BFDP prior probability		
Comparative model	No.	Z	*P*	OR (95% CI)	Heterogeneity chi-squared	*P*	I^2	Z	Begg's test	t	Egger's test	FPRP *P*-value[b]	FPRP statistical power[c]	0.25	0.1	0.01	0.001	0.0001	0.01	0.001	0.000001
4G4G/5G5G																					
Overall	7	0.31	0.755	1.042(0.805-1.348)	16.03	0.014	62.60%	1.8	0.072	1.06	0.336	0.754	0.997	0.694	0.872	0.987	0.999	1.000	0.998	1.000	1.000
Ethnicity																					
Caucasian	4	0.94	0.348	1.21(0.813-1.801)	11.25	0.01	73.30%					0.348	0.855	0.549	0.785	0.976	0.998	1.000	0.995	0.999	1.000
Asian	3	1.16	0.248	0.857(0.659-1.113)	3.34	0.189	40%					0.247	0.970	0.433	0.696	0.962	0.996	1.000	0.996	1.000	1.000
Source of control																					
HB	2	0.5	0.617	1.09(0.778-1.528)	0.04	0.848	0%					0.617	0.968	0.657	0.852	0.984	0.998	1.000	0.997	1.000	1.000
PB	3	1.23	0.22	0.906(0.774-1.061)	3.39	0.183	41.40%					0.221	1.000	0.398	0.665	0.956	0.995	1.000	0.997	1.000	1.000
4G4G/4G5G																					
Overall	7	1.23	0.217	1.070(0.961-1.192)	6.23	0.398	3.70%	1.2	0.23	−0.14	0.891	0.219	1.000	0.397	0.664	0.956	0.995	1.000	0.998	1.000	1.000
Ethnicity																					
Caucasian	4	2.03	0.042	1.142(1.005-1.297)	2.01	0.57	0.00%					0.041	1.000	**0.109**	0.269	0.802	0.976	0.998	0.991	0.999	1.000
Asian	3	0.91	0.364	0.911(0.744-1.115)	0.78	0.677	0.00%					0.366	0.999	0.524	0.767	0.973	0.997	1.000	0.997	1.000	1.000
Source of control																					
HB	2	1.03	0.315	1.16(0.873-1.541)	1.54	0.214	35.10%					0.306	0.962	0.488	0.741	0.969	0.997	1.000	0.996	1.000	1.000
PB	3	0.77	0.440	1.05(0.928-1.189)	3.74	0.154	46.50%					0.442	1.000	0.570	0.799	0.978	0.998	1.000	0.998	1.000	1.000
4G4G/4G5G+5G5G																					
Overall	7	0.82	0.409	1.044(0.943-1.155)	10.36	0.11	42.10%	1.8	0.072	0.46	0.662	0.404	1.000	0.548	0.784	0.976	0.998	1.000	0.999	1.000	1.000
Ethnicity																					
Caucasian	4	1.73	0.083	1.112(0.986-1.254)	4.74	0.192	36.70%					0.083	1.000	0.200	0.429	0.892	0.988	0.999	0.995	1.000	1.000
Asian	3	1.19	0.233	0.891(0.737-1.077)	1.88	0.39	0.00%					0.233	0.999	0.412	0.677	0.958	0.996	1.000	0.997	1.000	1.000
Source of control																					
HB	2	0.93	0.351	1.136(0.869-1.486)	0.94	0.332	0.00%					0.352	0.979	0.519	0.764	0.973	0.997	1.000	0.996	1.000	1.000
PB	3	0.42	0.676	0.957(0.78-1.175)	4.76	0.093	58.00%					0.675	1.000	0.669	0.859	0.985	0.999	1.000	0.998	1.000	1.000
4G4G+4G5G/5G5G																					
Overall	7	0.07	0.944	0.992(0.8-1.231)	14.54	0.024	58.70%	1.8	0.072	1.42	0.214	0.942	1.000	0.739	0.894	0.989	0.999	1.000	0.998	1.000	1.000
Ethnicity																					
Caucasian	4	0.46	0.643	1.088(0.763-1.55)	11.72	0.008	74.40%					0.640	0.962	0.666	0.857	0.985	0.998	1.000	0.997	1.000	1.000
Asian	3	0.8	0.423	0.909(0.721-1.147)	2.74	0.254	27%					0.421	0.996	0.559	0.792	0.977	0.998	1.000	0.997	1.000	1.000
Source of control																					
HB	2	0.11	0.913	0.985(0.743-1.304)	0.35	0.556	0%					0.916	0.997	0.734	0.892	0.989	0.999	1.000	0.997	1.000	1.000
PB	3	1.89	0.059	0.875(0.761-1.005)	1.34	0.512	0.00%					0.059	1.000	0.150	0.346	0.853	0.983	0.998	0.993	0.999	1.000

Abbreviations: OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based; FPRP, false positive report probability; BFDP, Bayesian False Discovery Probability.

[a]The results in bold represented there was statistically significant noteworthiness at 0.2 level by FPRP or 0.8 level by BFDP calculations.

[b]Chi-square test was used to calculate the genotype and haplotype frequency distributions.

[c]Statistical power was the power to detect an odds ratio of 1.5 for the homozygotes with the rare genetic variant and 1 for the heterozygotes and for the homozygote with the common variant.

Table 5. Stratified Analyses of the Rs2227631 and Rs2227667 Polymorphism on Cancer Risk.

No.	Comparative model	Z	*P*	OR (95% CI)	Heterogeneity			Begg's test		Egger's test		FPRP *P*-value[a]	FPRP statistical power[b]	FPRP prior probability					BFDP prior probability		
					Heterogeneity chi-squared	*P*	I^2	Z		t				0.25	0.1	0.01	0.001	0.0001	0.01	0.001	0.000001
	rs2227631																				
5	AA/GG	0.43	0.665	0.925(0.65-1.316)	15.46	0.004	74.10%	0.24	0.806	0.71	0.527	0.665	0.966	0.674	0.861	0.986	0.999	1.000	0.997	1.000	1.000
5	AA/AG	0.14	0.888	0.975(0.686-1.386)	18.71	0.001	78.60%	−0.24	1	0.46	0.68	0.869	0.994	0.724	0.887	0.989	0.999	1.000	0.997	1.000	1.000
5	AA/AG+GG	0.27	0.789	0.956(0.686-1.332)	18.68	0.001	78.60%	−0.24	1	0.53	0.635	0.790	0.983	0.707	0.879	0.988	0.999	1.000	0.997	1.000	1.000
5	AA+AG/GG	1.23	0.220	0.932(0.832-1.043)	1.23	0.874	0	0.73	0.462	1.18	0.323	0.220	1.000	0.398	0.664	0.956	0.995	1.000	0.998	1.000	1.000
5	GG/AA	0.43	0.665	1.081(0.760-1.538)	15.46	0.004	74.10%	0.24	0.806	−0.71	0.527	0.665	0.966	0.674	0.861	0.986	0.999	1.000	0.997	1.000	1.000
5	GG/GA	0.88	0.379	1.055(0.936-1.190)	0.98	0.913	0.00%	0.73	0.462	−0.48	0.665	0.383	1.000	0.535	0.775	0.974	0.997	1.000	0.998	1.000	1.000
5	GG/GA+AA	0.12	0.220	1.073(0.959-1.201)	1.23	0.874	0.00%	0.73	0.462	−1.18	0.323	0.220	1.000	0.398	0.665	0.956	0.995	1.000	0.998	1.000	1.000
5	GG+GA/AA	0.27	0.789	1.046(0.751-1.459)	18.68	0.001	78.6	−0.24	1.000	−0.53	0.635	0.791	0.983	0.707	0.879	0.988	0.999	1.000	0.997	1.000	1.000
	rs2227667																				
4	AA/GG	1.69	0.091	0.649(0.393-1.071)	21.76	0	86.20%	1.02	0.308	−1.88	0.201	0.091	0.458	0.373	0.641	0.951	0.995	0.999	0.986	0.999	1.000
4	AA/AG	0.11	0.911	0.980(0.687-1.398)	21.33	0	85.90%	-0.34	1	0.24	0.831	0.911	0.983	0.735	0.893	0.989	0.999	1.000	0.997	1.000	1.000
4	AA/AG+GG	0.97	0.333	0.889(0.701-1.128)	10.96	0.012	72.60%	−0.34	1	−0.49	0.674	0.333	0.991	0.502	0.751	0.971	0.997	1.000	0.997	1.000	1.000
4	AA+AG/GG	1.42	0.157	0.687(0.409-1.155)	29.77	0	89.90%	1.02	0.308	−1.25	0.338	0.157	0.545	0.463	0.721	0.966	0.997	1.000	0.990	0.999	1.000
4	GG/AA	1.69	0.091	1.541(0.933-2.546)	21.76	0	86.20%	1.02	0.308	−1.88	0.201	0.091	0.458	0.374	0.642	0.952	0.995	0.999	0.987	0.999	1.000
4	GG/GA	1.30	0.194	1.529(0.806-2.898)	40.1	0	92.5	−0.34	1	0.24	0.831	0.193	0.477	0.549	0.785	0.976	0.998	1.000	0.991	0.999	1.000
4	GG/GA+AA	1.42	0.157	1.455(0.866-2.445)	29.77	0	89.90%	1.02	0.308	−1.25	0.338	0.157	0.546	0.463	0.721	0.966	0.997	1.000	0.990	0.999	1.000
4	GG+GA/AA	0.97	0.333	1.124(0.887-1.426)	10.96	0.012	72.60%	−0.34	1	−0.49	0.674	0.336	0.991	0.504	0.753	0.971	0.997	1.000	0.997	1.000	1.000

Abbreviations: OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based; FPRP, false positive report probability; BFDP, Bayesian False Discovery Probability.

[a]Chi-square test was used to calculate the genotype and haplotype frequency distributions.

[b]Statistical power was the power to detect an odds ratio of 1.5 for the homozygotes with the rare genetic variant and 1 for the heterozygotes and for the homozygote with the common variant.

polymorphism, some results showed the evidence of publication bias (Egger's test for 4G4G vs 5G5G, 4G4G vs 4G5G, 4G4G vs 4G5G+5G5G, 4G4G+4G5G vs 5G5G: $P = 0.016/0.038/0.009/0.035$, Table 2). According to the SERPINE1 rs2227631/rs2227667 polymorphism, the results showed no evidence of publication bias (Table 5).

Sensitivity Analysis

None of the comparisons in the sensitivity analysis detected a change in the outcome of PAI-1 gene polymorphism, indicating that our results were statistically stable and reliable. The meta-regression found that ethnicity was the potential source of heterogeneity regarding the relationship between SERPINE1 rs2227631 polymorphism and cancer risk.

FPRP and BFDP Test

The FPRP values of statistical power for significant findings about the SERPINE1 rs1799889 polymorphism were shown in Table 2. According to the results of the FPRP analyses, almost all models of rs1799889 polymorphism were found to be noteworthy by FPRP estimation at the OR of 1.5 with the prior probability of 0.25 and 0.1, but there were no noteworthy by BFDP test at the OR of 1.5 with the prior probability of 0.01, 0.001 and 0.000001, which suggested that the results of this study should be interpreted with caution.

Discussion

Cancer was a significant economic burden for public health systems worldwide. Up to now, a great deal of research has shown that cancer might be closely related to genetic factors. PAI-1 polymorphisms were considered to be closely related to cancer development and outcome among different individuals,[2,48] since genetic variations had an essential impact on the activities of PAI-1. In regard to the PAI-1 gene, the polymorphism about rs1799889, rs2227631 and rs2227667 have been the most frequently studied, but the conclusion was controversial about judging the relationship between PAI-1 polymorphism and cancer risk which was estimated in our present study by aggregating the findings of overall qualified case-controlled studies.

Our present study found that the SERPINE1 rs1799889 polymorphism was statistically related with cancer risk, but there was no association observed for rs2227631 and rs2227667 polymorphism. Furthermore, the rs1799889 polymorphism was found to have higher risks for breast, endometrial and colorectal cancer, but there was no effect on susceptibility to uterine cervical cancer.[19,22,31,34] However, the linkage disequilibrium analysis detected that both 4G for PAI-1 rs1799889 and A for TGF-β1 rs1800468 pair-haplotype was in strong linkage disequilibrium with a statistically increased risk to uterine cervical cancer.[34] Meanwhile, the linkage disequilibrium analysis detected that both 4G4G for PAI-1 rs1799889 and CC for uPARs 4065 pair-haplotype was in strong linkage disequilibrium with a statistically increased risk to cervical neoplasia.[30] The polymorphism of rs2227631 was found to have higher risks for breast cancer and glioblastoma, but there was no effect on susceptibility to ovarian and gastric cancer.[23,38,44,45] The polymorphism of rs2227667 was at higher risks for breast cancer and multiple myeloma, while no effect was found in gastric cancer.[44-47] PAI-1 gene-polymorphism exerted different impacts on different organs, maybe thereby increasing the persons who had a specific inherited predisposition to cancer, but the mechanism was not entirely clear. According to our present meta-analysis, PAI-1 gene-polymorphism in different locations maybe have different distributions to different types of cancers.

Concerning stratified analysis by ethnicity about rs1799889, our present meta-analysis found an ascending risk in 4G carriers among the Caucasian and Asian population but not mixed population for these types of cancers. For masticatory and gastrointestinal cancer, no significantly increased risk was found. Moreover, there was a statistically increased risk of gynecological cancer in both Caucasian and Asian population, potential explanations for this result included 3 aspects: (1) wide difference in incidence rates of gene polymorphisms existed in disparate ethnic populations[49]; (2) wide difference in susceptibility to different cancers existed in people in different parts of the world; (3) some objective factors might also have some effect such as sample size, selection bias, inclusion or exclusion criteria and so on. Therefore, a big population study with multiple analyses was needed to conduct and further prove the relationship between rs1799889 polymorphism and cancer risks.

When interpreting the pooled findings in our present meta-analysis, there were some restrictions that should be mentioned. Firstly, although we had detected a comprehensive and thorough search, the count of studies and participant studies were not adequate, especially for rs2227631 and rs2227667. Secondly, there was no further analysis of the underlying correlation between gene and behavior, environment, prognosis, or linkage disequilibrium and so on, because common raw data was missing. Thirdly, most research mainly focused on polymorphism (rs1799889) and tiny minority research focused on rs1799768, both of which located in the promoter region −675 bp.[50] However, rs1799768 polymorphism located in the SERPINE1 promoter was genotyped.[44] Based on the controversy above mentioned, we had to exclude the research about rs1799768. Finally, the meta-analysis revealed some statistically significant results in Egger's test which suggested the existence of the publication bias, hence, the corresponding results should be interpreted cautiously.

Through a review of the literature, we found that 2 similar articles had been published in the past.[50,51] Compared with these articles, the following contents were added to our study: (1) relevant research literatures after 2013 were added; (2) the feminine, masticatory and gastrointestinal cancer subgroups were compared and analyzed; (3) 2 more sites of rs2227631 and rs2227667 polymorphisms were added.

Our study finally reached a conclusion that PAI genetic polymorphism (rs1799889) might be connected with the predisposition of cancer, especially feminine cancer. Moreover, the increased cancer risks were observed in Caucasians group. No significant association was identified for the rs2227631 and rs2227667 polymorphisms with cancer risk. Furthermore, rs1799889 polymorphism may be a potential marker genotyping to cancer susceptibility for clinical assessment.

Authors' Note

Our study did not require an ethical board approval because it did not contain human or animal trials.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The present study was supported in part by the Natural Science Foundation of Guangxi Province (Grant No.: 2018GXNSFAA138003).

ORCID iD

Cuiping Li, PhD https://orcid.org/0000-0002-9483-6452

References

1. Schork NJ, Fallin D, Lanchbury S. Single nucleotide polymorphisms and the future of genetic epidemiology. *Clin Genet*. 2000; 58(0009-9163):250-264.
2. Jevric M, Matić IZ, Krivokuća A, et al. Association of uPA and PAI-1 tumor levels and 4G/5G variants of PAI-1 gene with disease outcome in luminal HER2-negative node-negative breast cancer patients treated with adjuvant endocrine therapy. *BMC Cancer*. 2019;19(1):71.
3. Pepper MS. Role of the matrix metalloproteinase and plasminogen activator-plasmin systems in angiogenesis. *Arterioscler Thromb Vasc Biol*. 2001;21(7):1104-1117.
4. Ulisse S, Baldini E, Sorrenti S, D'Armiento M. The urokinase plasminogen activator system: a target for anti-cancer therapy. *Curr Cancer Drug Targets*. 2009;9(1):32-71.
5. Madunic J. The urokinase plasminogen activator system in human cancers: an overview of its prognostic and predictive role. *Thromb Haemost*. 2018;118(12):2020-2036.
6. Jaiswal RK, Varshney AK, Yadava PK. Diversity and functional evolution of the plasminogen activator system. *Biomed Pharmacother*. 2018;98:886-898.
7. de la Cruz-Mosso U, Elena Ramos-Arellano L, Francisco Muñoz-Valle J, et al. PAI-1 haplogenotype confers genetic susceptibility for obesity and hypertriglyceridemia in Mexican children. *Invest Clin*. 2016;57(3):246-258.
8. El Edel RH, Essa ES, Essa AS, Hegazy SA, El Rowedy DI. Serum PAI-1 and PAI-1 4G/5G polymorphism in hepatitis C virus-induced cirrhosis and hepatitis C virus-induced hepatocellular carcinoma patients. *Viral Immunol*. 2016;29(9):510-515.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7): e1000097.
10. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst*. 2004;96(6):434-442.
11. Wakefield J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am J Hum Genet*. 2007;81(2):208-227.
12. Turkmen B, Schmitt M, Schmalfeldt B, et al. Mutational analysis of the genes encoding urokinase-type plasminogen activator (uPA) and its inhibitor PAI-1 in advanced ovarian cancer. *Electrophorcsis*. 1997;18(5):686-689.
13. Smolarz B, Blasiak J, Pytel J, Romanowicz-Makowska H, Zadrozny M. 4G/5G polymorphism in the promoter of Plasminogen Activator Inhibitor-1 (PAI-1) gene in subjects with node-negative and node-positive breast cancer. *Med Sci Monit*. 1999;5(5):833-837.
14. Blasiak J, Smolarz B. Plasminogen activator inhibitor-1 (PAI-1) gene 4G/5G promoter polymorphism is not associated with breast cancer. *Acta Biochimica Polonica*. 2000;47(1):191-199.
15. Loktionov A, Watson MA, Stebbings WS, Speakman CT, Bingham SA. Plasminogen activator inhibitor-1 gene polymorphism and colorectal cancer risk and prognosis. *Cancer Letters*. 2003;189(2):189-196.
16. Zhou X, Xia S. The study of the PAI-I activity and its promotor region gene polymorphism in ovarian cancer (in Chinese). *Guangzhou Med J*. 2005;29(12):1072-1075.
17. Liming Z, Xj Z. Relationship between the 4G/5G polymorphism of the plasminogen activator inhibitor-1 gene and the acute leukemia (in Chinese). *J Leukem Lymphoma*. 2005;14(5):302-304.
18. Sternlicht MD, Dunning AM, Moore DH, et al. Prognostic value of PAI1 in invasive breast cancer: evidence that tumor-specific factors are more important than genetic variation in regulating PAI1 expression. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(11):2107-2114.
19. Forsti A, Lei H, Tavelin B, et al. Polymorphisms in the genes of the urokinase plasminogen activation system in relation to colorectal cancer. *Ann Oncol*. 2007;18(12):1990-1994.
20. Woo M, Park K, Nam J, Kim JC. Clinical implications of matrix metalloproteinase-1, -3, -7, -9, -12, and plasminogen activator inhibitor-1 gene polymorphisms in colorectal cancer. *J Gastroenterol Hepatol*. 2007;22(7):1064-1070.
21. Minisini AM, Fabbro D, Di Loreto C, et al. Markers of the uPA system and common prognostic factors in breast cancer. *Am J Clin Pathol*. 2007;128(1):112-117.
22. Lei H, Hemminki K, Johansson R, et al. PAI-1-675 4G/5G polymorphism as a prognostic biomarker in breast cancer. *Breast Cancer Res Treat*. 2008;109(1):165-175.
23. Bentov Y, Brown TJ, Akbari MR, et al. Polymorphic variation of genes in the fibrinolytic system and the risk of ovarian cancer. *PLoS One*. 2009;4(6):e5918.
24. Palmirotta R, Ferroni P, Savonarola A, et al. Prognostic value of pre-surgical plasma PAI-1 (plasminogen activator inhibitor-1) levels in breast cancer. *Thromb Res*. 2009;124(4):403-408.

25. Weng CJ, Tsai CM, Chen YC, et al. Evaluation of the association of urokinase plasminogen activator system gene polymorphisms with susceptibility and pathological development of hepatocellular carcinoma. *Ann Surg Oncol*. 2010;17(12):3394-3401.
26. Su CK, Yeh KT, Yeh CB, et al. Genetic polymorphism of the plasminogen activator inhibitor-1 is associated with an increased risk of endometrial cancer. *J Surg Oncol*. 2011;104(7):755-759.
27. Vossen CY, Hoffmeister M, Chang-Claude JC, Rosendaal FR, Brenner H. Clotting factor gene polymorphisms and colorectal cancer risk. *J Clin Oncol*. 2011;29(13):1722-1727.
28. Weng CJ, Lin CW, Chung TT, Tsai CM, Chen MK, Yang SF. Impact of uPA system gene polymorphisms on the susceptibility of environmental factors to carcinogenesis and the development of clinicopathology of oral cancer. *Ann Surg Oncol*. 2011;18(3): 805-812.
29. Onur E, Kurdal AT, Tugrul B, et al. Is genetic screening necessary for determining the possibility of venous thromboembolism in cancer patients? *Med Princ Pract*. 2012;21(2):160-163.
30. Tee YT, Wang PH, Tsai HT, et al. Genetic polymorphism of urokinase-type plasminogen activator is interacting with plasminogen activator inhibitor-1 to raise risk of cervical neoplasia. *J Surg Oncol*. 2012;106(2):204-208.
31. Gilabert-Estellés J, Ramón LA, Braza-Boïls A, et al. Plasminogen activator inhibitor-1 (PAI-1) 4 G/5 G polymorphism and endometrial cancer. Influence of PAI-1 polymorphism on tissue PAI-1 antigen and mRNA expression and tumor severity. *Thromb Res*. 2012;130(2):242-247.
32. Divella R, Mazzocca A, Gadaleta C, et al. Influence of plasminogen activator inhibitor-1 (SERPINE1) 4G/5G polymorphism on circulating SERPINE-1 antigen expression in HCC associated with viral infection. *Cancer Genomics Proteomics*. 2012;9(4): 193-198.
33. Vylliotis A, Yapijakis C, Nkenke E, et al. Effect of thrombosis-related gene polymorphisms upon oral cancer: a regression analysis. *Anticancer Res*. 2013;33(9):4033-4040.
34. Ramos-Flores C, Romero-Gutiérrez T, Delgado-Enciso I, et al. Polymorphisms in the genes related to angiogenesis are associated with uterine cervical cancer. *Int J Gynecol Cancer*. 2013;23(7): 1198-1204.
35. Ozen F, Erdis E, Sik E, Silan F, Uludag A, Ozdemir O. Germ-line MTHFR C677T, FV H1299R and PAI-1 5G/4G variations in breast carcinoma. *Asian Pac J Cancer Prev*. 2013;14(5):2903-2908.
36. Bayramoglu A, Gunes HV, Metintas M, et al. Plasminogen activator inhibitor-1 and susceptibility to lung cancer: a population genetics perspective. *Genet Test Mol Biomarkers*. 2014;18(8): 587-590.
37. Mitrovic M, Suvajdzic N, Elezovic I, et al. Thrombotic events in acute promyelocytic leukemia. *Thromb Res*. 2015;135(4): 588-593.
38. Pooyan H, Ahmad E, Azadeh R. 4G/5G and A-844G polymorphisms of plasminogen activator inhibitor-1 associated with glioblastoma in Iran—a case-control study. *Asian Pac J Cancer Prev*. 2015;16(15):6327-6330.
39. Karakuş S, Kurtulgan HK, Kılıçgün H, Erşan S, Bakır S. The association of plasminogen activator inhibitor type 1 (PAI-1) level and PAI-1 4G/5G gene polymorphism with the formation and the grade of endometrial cancer. *Biochem Genet*. 2017;55(4):314-321.
40. Rui Z, Lu M, Fei C. Correlation between the plasma concentrations of u-PA and PAI-1 and the 4G/5G polymorphism of PAI-1 and the patients with naso-pharyngeal carcinoma (in Chinese). *J Med Res*. 2018;47:39-42.
41. Oh J, An HJ, Kim JO, et al. Association between five common plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms and colorectal cancer susceptibility. *Int J Mol Sci*. 2020;21(12): 4334.
42. Pouladi N, Shavali M, Abdolahi S. Combined genotype effects of TP53 and PAI-1 polymorphisms in breast cancer susceptibility: multifactor dimensionality reduction and in silico analysis. *Hum Hered*. 2020;85(2):51-60.
43. Bi Y, Zheng M, Liang W. The correlation between 4G/5G polymorphism located in the promoter region of PAI-I gene and breast cancer (in Chinese). *Chin J Birth Health Heredity*. 2004;12(1): 26-27.
44. Ju H, Lim B, Kim M, et al. SERPINE1 intron polymorphisms affecting gene expression are associated with diffuse-type gastric cancer susceptibility. *Cancer*. 2010;116(18):4248-4255.
45. Chen YL, Jia YM, Xie YT, Li Y, Fang WG, Tian XX. Association of single nucleotide polymorphisms in PAI-1 with breast cancer susceptibility and prognosis (in Chinese). *Chin J Pathol*. 2016; 45(8):533-539.
46. Purdue MP, Lan Q, Menashe I, et al. Variation in innate immunity genes and risk of multiple myeloma. *Hematol Oncol*. 2011;29(1): 42-46.
47. Martino A, Campa D, Jurczyszyn A, et al. Genetic variants and multiple myeloma risk: IMMEnSE validation of the best reported associations—an extensive replication of the associations from the candidate gene era. *Cancer Epidemiol Biomarkers Prev*. 2014;23(4):670-674.
48. Divella R, Daniele A, Abbate I, et al. Circulating levels of PAI-1 and SERPINE1 4G/4G polymorphism are predictive of poor prognosis in HCC patients undergoing TACE. *Transl Oncol*. 2015; 8(4):273-278.
49. Chauhan T, Mittal RD, Mittal B. Association of common single nucleotide polymorphisms of candidate genes with gallstone disease: a meta-analysis. *Indian J Clin Biochem*. 2020;35(3): 290-2311.
50. Xu X, Xie Y, Lin Y, et al. PAI-1 promoter 4G/5G polymorphism (rs1799768) contributes to tumor susceptibility: evidence from meta-analysis. *Exp Ther Med*. 2012;4(6):1127-1133.
51. Wang S, Cao Q, Wang X, et al. PAI-14G/5G polymorphism contributes to cancer susceptibility: evidence from meta-analysis. *PLoS One*. 2013;8(2):e56797.