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RESEARCH ARTICLE

Association of lncRNA *PRNCR1* polymorphisms with cancer susceptibility: a meta-analysis of the current literature

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Abstract. Considerable studies exploring the relevance of single-nucleotide polymorphisms (SNPs) in the prostate cancer noncoding RNA 1 (*PRNCR1*) gene with various cancer susceptibilities have obtained debatable results. This meta-analysis was performed to precisely assess this association. Relevant published studies were selected by retrieving studies from PubMed, Embase, Web of Science, CNKI and Chinese Wanfang databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were applied to evaluate the strength of *PRNCR1* polymorphisms correlated with cancer susceptibility. A total of 12 articles, containing 40 independent case–control studies and seven SNPs (rs1016343, rs13252298, rs16901946, rs7007694, rs1456315, rs13254738 and rs7463708), were ultimately included in our meta-analysis. Summary results revealed a significant association with an increased overall risk of cancer for the rs1016343 C>T polymorphism (T vs C: OR=1.19, 95% CI=1.02–1.39; TT+CT vs CC: OR= 1.25, 95% CI=1.05–1.49) and rs16901946 A>G polymorphism (G vs A: OR=1.17, 95% CI=1.09–1.27; GG+AG vs AA: OR=1.20, 95% CI=1.09–1.32). Moreover, evidence of the rs13252298 A>G polymorphism correlation with decreased overall risk of cancer was observed (GG vs AG+AA: OR=0.78, 95% CI =0.67–0.92). Subgroup analyses by cancer type and ethnicity also revealed that the rs1016343 C>T polymorphism was linked with an increased risk of prostate cancer and Caucasians, respectively. The rs13252298 A>G polymorphism was correlated with a decreased risk of colorectal cancer and prostate cancer. The rs16901946 A>G polymorphism was related to an increased risk of gastric cancer and colorectal cancer in Asians. Additionally, the rs13254738 A>C polymorphism was correlated with reduced cancer risk in Asians. No correlations were discovered with cancer risk in rs7007694 T>C, rs7463708 T>G, and rs1456315 A>G polymorphisms. In summary, our meta-analysis indicates that *PRNCR1* rs1016343, rs16901946 and 13252298 polymorphisms are associated with cancer susceptibility. Further large-scale studies are required to certify our findings.

Keywords. lncRNA; *PRNCR1* gene; polymorphisms; cancer; susceptibility; meta-analysis.

Introduction

Cancer has become a main public health problem worldwide and is considered to be the second leading cause of mortality after cardio-cerebrovascular disease (Wang *et al.* 2019). Based on GLOBOCAN 2018 report, ∼18.1 million patients were diagnosed with cancer, of which 9.6 million died (Ferlay *et al.* 2019). However, the mechanisms contributing to cancer pathogenesis are still unclear. Various factors are supposed to play a role in carcinogenesis, such as environment, genetic, chronic inflammation, viral infection, unhealthy eating habits and lifestyles, and so on (Romani *et al.* 2015; Khawar *et al.* 2016; Wang and Palefsky 2016). Among them, genetic factors are considered to be one of the common factors of cancer incidence, and numerous genes have been ascertained as cancer-susceptible genes (Ponder 2001; Dong *et al.* 2008).

Long-noncoding RNAs (lncRNAs), which are single-stranded noncoding RNAs with lengths of over 200 nucleotides and no ability to encode proteins, play critical

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roles in many vital biological processes, including epigenetics, stress response, cell cycle, cell differentiation and cell apoptosis (Fatica and Bozzoni 2014; Do and Kim 2018). LncRNAs participate in these processes due to their ability to regulate gene expression at various levels through chromatin remodelling and transcriptional and posttranscriptional mechanisms (Mercer *et al.* 2009; Guttman and Rinn 2012). Recently, mounting evidence has shown that lncRNAs are involved in tumourigenesis and progression as proto-oncogenes or anti-oncogenes, and the abnormal expression of lncRNAs is closely related to the occurrence of cancer (Chung *et al.* 2011; Uszczynska-Ratajczak *et al.* 2018). To date, lncRNAs of over 50,000 have been identified in the human genome, and extensive research has been conducted on the effect of lncRNAs on human diseases, especially cancer (Uszczynska-Ratajczak *et al.* 2018).

Prostate cancer noncoding RNA 1 (*PRNCR1*), also named *PCAT8* and *CARLo3*, is an intron-free lncRNA of ∼13 kb that is mapped to the 'genetic desert' region of chromosome 8q24 (128.14–128.28 Mb) (Chung *et al.* 2011). Previous studies have demonstrated that *PRNCR1* promotes carcinogenesis of the prostate by binding to the androgen receptor (AR) (Yang *et al.* 2013). Emerging studies have suggested that aberrant expression of *PRNCR1* is closely related to the occurrence of various cancers (Yang *et al.* 2016; Cheng *et al.* 2018; Guo *et al.* 2019). In addition, the application of genomewide association studies (GWAS) allowed us to further understand the association of genetic variation with cancer. Single-nucleotide polymorphisms (SNPs) are one of the most universal genetic variations in lncRNAs, may directly or indirectly influence the expression and function of lncRNAs through a variety of pathways and are involved in the genesis and development of cancer (Cheetham *et al.* 2013; Yang *et al.* 2019). Some original studies and even three meta-analyses have investigated the correlation of *PRNCR1* SNPs with various cancer susceptibilities. However, the obtained results are still controversial and inconclusive. Further, some newly published studies have provided the basis for renovating datasets and more precisely assessing this association. Therefore, we conducted this updated meta-analysis of all available data to detect the accurate relationship of *PRNCR1* polymorphisms with cancer susceptibility.

Methods

Publication search

Two independent investigators (PD and GYL) conducted a comprehensive literature search limited to the English or Chinese language in PubMed, Embase, Web of Science, CNKI and Chinese Wanfang databases (up to 10 April 2020). The search keywords used were as follows: 'cancer or neoplasms or carcinoma or tumor' and '*PRNCR1* or prostate cancer non-coding RNA 1 or *PCAT8* or *CARLo3*' and 'polymorphisms or variants or variation or SNP or single nucleotide polymorphism'. References in the included publications were also hand-searched for potentially relevant articles. Eligible studies met the following criteria: (i) case–control studies evaluating the relationship of *PRNCR1* SNPs with cancer susceptibility; (ii) adequate genotype data of each included *PRNCR1* SNP; (iii) at least two studies for each involved *PRNCR1* polymorphism; and (iv) genotype frequencies in controls in conformance with Hardy–Weinberg equilibrium (HWE). The exclusion criteria were as follows: (i) duplicate studies, meeting abstracts, case reports, meta-analyses, and reviews; (ii) no sufficiency to genotype information; and (iii) no relevance to *PRNCR1* polymorphisms or cancer susceptibility.

Data extraction

Data extraction was conducted independently by two investigators (PD and JSZ), and any disparities were resolved by consensus with a third reviewer (YL). For each included article, the collected information included first author, publication year, country, tumour type, ethnicity, source of control, genotype method, sample size, genotype of SNPs, genotype distribution, minor allele frequency (MAF) in controls, *P*-value of HWE in controls, and Newcastle–Ottawa Scale (NOS) score. Articles covering more than one polymorphism were classified as including different studies, and data were extracted according to each SNP. We categorized ethnicities as either Asian or Caucasian. If a study contained subjects from different populations, we extracted data for each ethnic group separately.

Methodology quality assessment

The study quality was separately assessed by two investigators (PD and YTL) based on the NOS (Oremus *et al.* 2012). This method evaluated the quality of a study based on three perspectives: selection (0–4), comparability (0–2), and exposure (0–3). The scale scores ranged from 0 to 9. Publications with total scores of 0–4 and 5–9 were regarded as poor-quality and high-quality studies, respectively. Publications with NOS scores ≥5 points were enrolled in this study.

Statistical analysis

The correlated strength between *PRNCR1* SNPs and cancer susceptibility was analysed using odds ratios (ORs) with 95% confidence intervals (CIs) of three genetic models. For the *PRNCR1* rs13252298 A>G polymorphisms, the pooled ORs were calculated for the allele model (G vs A), dominant model (GG+AG vs AA), and recessive model (GG vs AG+AA). Similar genetic models were also adopted for the

PRNCR1 rs1016343 C>T, rs16901946 A>G, rs7007694 T>C, rs1456315 A>G, rs13254738 A>C, rs13254738 A>C and rs7463708 T>G variants. The HWE test was carried out for genotypes of control subjects using the chi-square test, and $P<0.05$ be regarded as significant disequilibrium. Cochran's Q-test and I^2 statistics were adopted to evaluate between-study heterogeneity. When $P<0.05$ (Q test) or $I^2>50\%$, heterogeneity was considered to be significant (Mantel and Haenszel 1959). The random-effects model was applied to the combined analysis if significant heterogeneity existed. Otherwise, a fixed-effects model was chosen. Stratified analysis by cancer type and ethnicity was further conducted to evaluate the possible origin of heterogeneity. Sensitivity analysis was performed by excluding one eligible study each time. Begg's and Egger's tests were utilized to detect publication bias. All statistical analyses were carried out by STATA 15.1 (Stata Corporation, College Station, USA), with $P<0.05$ (two-sided) implying statistical significance.

Results

Characteristics of the eligible studies

A total of 82 potentially relevant articles were identified by a systematic database search. After the removal of duplicate items, 43 articles were included for a systematic review. Further screening led to the removal of 31 articles due to different deficiencies. As shown in figure 1; 12 of them were finally selected for this meta-analysis (Salinas *et al.* 2008; Zheng *et al.* 2010; Chung *et al.* 2011; Li *et al.* 2013, 2016; Hui *et al.* 2014; He *et al.* 2017; Sattarifard *et al.* 2017; Yang *et al.* 2018; AlMutairi *et al.* 2019; Hong *et al.* 2019; Zhou *et al.* 2019). Table 1 summed up the characteristics of the enrolled studies. Of the 12 articles, nine were conducted among Asians, and three were performed among Caucasians. The sources of the controls of 10 articles were hospital-based populations, and two articles were population-based populations. Genotyping methods included MassARRAY (four articles), PCR-restriction fragment length polymorphism (RFLP) (three articles), TaqMan (two articles), PCR-high resolution melting (HRM) (one article), SNPlex Genotyping System (one article) and Multiplex PCR-based Invader Assay (one article). There were five articles on prostate cancer, four on gastric cancer, and three on colorectal cancer. The NOS score of each enrolled article was between 6 and 8 points, suggesting that they were of high quality (table 1). The genotype frequency distributions of all eight SNPs in *PRNCR1* genes from 12 articles are shown in table 2. After five case–control studies that did not meet the Hardy–Weinberg balance ($P_{HWH}<0.05$) were excluded. Thus, 12 eligible articles, containing 40 case–control studies and seven *PRNCR1* SNPs were involved in our final calculation.

Meta-analysis

***PRNCR1 rs1016343 C>T polymorphism and cancer risk*:** A total of eight studies, comprising 4434 cases and 4691 controls were examined for the relationship between the *PRNCR1* rs1016343 C>T polymorphism and cancer risk. The pooled results found that rs1016343 was significantly associated with an increased overall risk of cancer (T vs C: OR=1.19, 95% CI=1.02–1.39; TT+CT vs CC: OR=1.25, 95% CI=1.05–1.49) (figure 1, a&b; table 2). Further, subgroup analysis by cancer type and ethnicity found that rs1016343 was related to increased risk of prostate cancer (T vs C: OR=1.42, 95% CI=1.29–1.56; TT+CT vs CC: OR=1.47, 95% CI=1.22–1.78; TT vs CT+CC: OR=1.83, 95% CI=1.53–2.18), and the increased cancer risk was also observed among Caucasians (T vs C: OR=1.33, 95% CI =1.17–1.52; TT+CT vs CC: OR=1.35, 95% CI=1.14–1.60; TT vs CT+CC: OR=1.70, 95% CI=1.21–2.40) (table 2).

***PRNCR1 rs13252298 A>G polymorphism and cancer risk*:** Eight studies involving 3298 cases and 3773 controls were used to assess the association of the *PRNCR1* rs13252298 A>G polymorphism with cancer susceptibility. In the overall analysis, a significant correlation with decreased cancer risk was observed in the recessive model (GG vs AG +AA: OR=0.78, 95% CI=0.67–0.92) (figure 2c; table 2). Stratification analyses based on cancer type and ethnicity revealed a significantly reduced risk of cancer in the colorectal cancer subgroup (G vs A: OR=0.79, 95% CI=0.66–0.94; GG +AG vs AA: OR=0.75, 95% CI=0.59–0.94) and prostate cancer subgroup (GG vs AG+AA: OR=0.72, 95% CI=0.58–0.89) (table 2).

***PRNCR1 rs16901946 A>G polymorphism and cancer risk*:** The relationship of the *PRNCR1* rs16901946 A>G polymorphism with cancer risk was investigated in eight studies involving 3461 cancer patients and 3874 controls. The rs16901946 exhibited a significant association with increased overall cancer risk (G vs A: OR=1.17, 95% CI=vs AA: OR1.09–1.27; GG+AG vs AA: OR=1.20, 95% CI=1.09–1.32) (figure 2, d&e; table 2). We further evaluated the effect of rs16901946 on cancer risk by subgroup analyses. In analyses by cancer type, rs16901946 was significantly associated with an increased risk of gastric cancer (G vs A: OR=1.17, 95% CI=1.04–1.32; GG+AG vs AA: OR=1.29, 95% CI=1.12–1.49) and colorectal cancer (GG vs AG+AA: OR=1.75, 95% CI=1.01–3.04). In analyses according to ethnicity, rs16901946 was observed to increase cancer risk among Asians (G vs A: OR=1.17, 95% CI =1.09–1.26; GG+AG vs AA: OR=1.20, 95% CI=1.09–1.32) (table 2).

***PRNCR1 rs7007694 T>C, rs1456315 A>G, rs13254738 A>C and rs7463708 T>G polymorphisms and cancer risk*:** The relationship of the *PRNCR1* rs16901946 A>G polymorphism

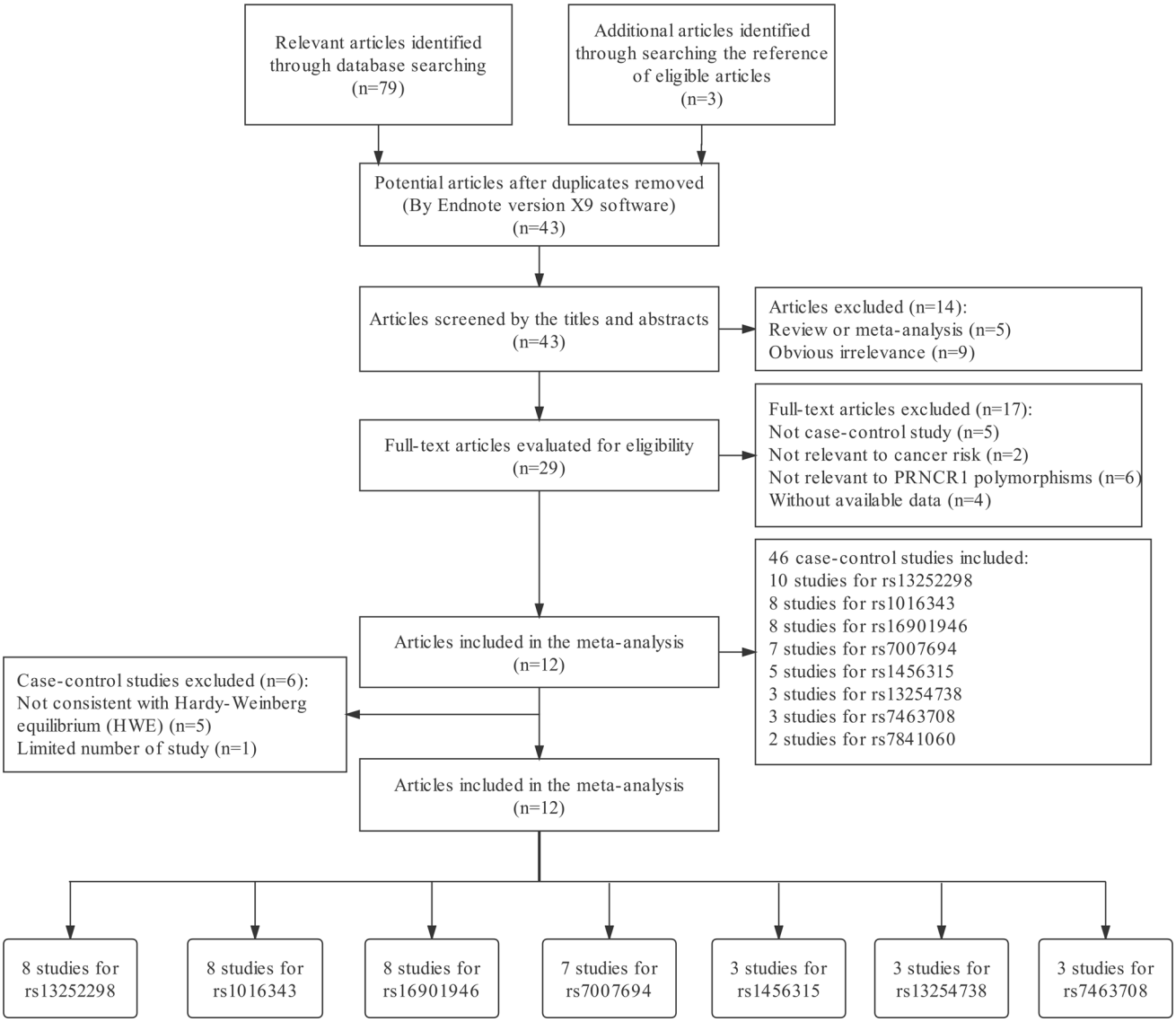

Figure 1. Flow diagram of the study selection process.

with cancer risk was investigated in eight studies involving 3461 cancer patients and 3874 controls. rs16901946 exhibited a significant association with increased overall cancer risk (G vs A: OR=1.17, 95% CI=1.09–1.27; GG+AG vs AA: OR=1.20, 95% CI=1.09–1.32) (figure 2, d&e; table 2). We further evaluated the effect of rs16901946 on cancer risk by subgroup analyses. In analyses by cancer type, rs16901946 was significantly associated with an increased risk of gastric cancer (G vs A: OR=1.17, 95% CI=1.04–1.32; GG+AG vs AA: OR=1.29, 95% CI=1.12–1.49) and colorectal cancer (GG vs AG+AA: OR=1.75, 95% CI=1.01–3.04). In analyses according to ethnicity, rs16901946 was observed to increase cancer risk among Asians (G vs A: OR=1.17, 95% CI =1.09–1.26; GG+AG vs AA: OR=1.20, 95% CI=1.09–1.32) (table 2).

Heterogeneity and sensitivity analysis

The results of the heterogeneity assessment showed inter-study heterogeneity across studies in the overall and/or subgroup analyses (table 2). We further implemented sensitivity analyses by ignoring studies one at a time to explore the effect of each study on the pooled results. After the removal of individual studies, some pooled ORs and 95% CIs showed significant changes (table 3).

Publication bias

Begg's and Egger's tests evaluated publication bias. There was an absence of significant publication bias in any of the genetic models for all seven *PRNCR1* SNPs, which suggested that our results were reliable (figure 3; table 2).

Table 1. Characteristics of included studies on *PRNCR1* polymorphisms and cancer susceptibility included in the meta-analysis.

First author	Year	Country	Ethnicity	Tumour type	Source of control	Genotype method	Sample size (cases/control)	Genotyping distribution						MAF in control	HWE(P)	NOS
								Case			Control					
rs1016343(C/T)								CC	CT	TT	CC	CT	TT			
Salinas CA	2008	USA	Caucasian	Prostate cancer	PB	SNPlex	1253/1233	711	454	88	796	385	52	0.198	0.528	8
Zheng SL	2010	China	Asian	Prostate cancer	PB	MassARRAY	284/147	76	159	49	66	65	16	0.330	0.999	8
Chung S	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1502/1552	650	667	185	841	608	103	0.262	0.624	6
Li L	2013	China	Asian	Colorectal cancer	HB	PCR-RFLP	313/595	117	156	40	227	276	92	0.387	0.593	7
Hui J	2014	China	Asian	Prostate cancer	HB	PCR-HRM	284/284	103	118	63	108	134	42	0.384	0.967	7
Li L	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	219/394	78	109	32	140	176	78	0.421	0.094	8
Hong JH	2019	Korea	Asian	Gastric cancer	HB	TaqMan	437/357	209	191	37	171	158	28	0.300	0.305	6
AlMutairi M	2019	Saudi Arabia	Caucasian	Colorectal cancer	HB	TaqMan	142/129	100	37	5	92	34	3	0.155	0.946	7
rs13252298(A/G)								AA	AG	GG	AA	AG	GG			
Chung S	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1501/1550	808	556	137	609	737	204	0.369	0.416	6
Li L	2013	China	Asian	Colorectal cancer	HB	PCR-RFLP	313/595	166	121	26	264	270	61	0.329	0.508	7
Hui J	2014	China	Asian	Prostate cancer	HB	PCR-HRM	277/267	147	103	27	135	111	21	0.287	0.783	7
Li L	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	219/394	88	107	24	198	161	35	0.293	0.781	8
He BS	2017	China	Asian	Gastric cancer	HB	MassARRAY	494/494	236	215	43	209	235	50	0.339	0.173	8
Sattarifard H	2017	Iran	Caucasian	Prostate cancer	HB	PCR-RFLP	178/179	33	107	38	25	141	13	0.466	0.000[a]	7
Yang XB	2018	China	Asian	Gastric cancer	HB	MassARRAY	300/300	135	133	32	125	141	34	0.348	0.541	8
Zhou HC	2019	China	Asian	Colorectal cancer	HB	MassARRAY	50/50	21	25	4	19	23	8	0.390	0.814	8
Hong JH	2019	Korea	Asian	Gastric cancer	HB	TaqMan	437/357	214	182	41	158	171	28	0.318	0.048[a]	6
AlMutairi M	2019	Saudi Arabia	Caucasian	Colorectal cancer	HB	TaqMan	144/123	74	59	11	58	51	14	0.321	0.586	7
rs16901946(A/G)								AA	AG	GG	AA	AG	GG			
Chung S	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1504/1554	690	637	177	783	645	126	0.289	0.671	6
Li L	2013	China	Asian	Colorectal cancer	HB	PCR-RFLP	313/595	175	117	21	338	232	25	0.237	0.056	7
Li L	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	219/394	125	92	2	230	135	29	0.245	0.144	8
He BS	2017	China	Asian	Gastric cancer	HB	MassARRAY	494/494	261	203	30	301	176	17	0.213	0.153	8
Yang XB	2018	China	Asian	Gastric cancer	HB	MassARRAY	300/300	155	125	20	186	104	10	0.207	0.322	8
Zhou HC	2019	China	Asian	Colorectal cancer	HB	MassARRAY	50/50	36	7	7	26	21	3	0.270	0.644	8
Hong JH	2019	Korea	Asian	Gastric cancer	HB	TaqMan	437/357	208	191	38	178	147	32	0.296	0.834	6
AlMutairi M	2019	Saudi Arabia	Caucasian	Colorectal cancer	HB	TaqMan	144/130	140	4	0	128	2	0	0.008	0.929	7
rs7007694(T/C)								TT	TC	CC	TT	TC	CC			
Chung S	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1497/1554	656	650	191	700	684	170	0.329	0.880	6
Li L	2013	China	Asian	Colorectal cancer	HB	PCR-RFLP	313/595	184	107	22	362	208	25	0.217	0.474	7
Li L	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	219/394	142	72	5	214	159	21	0.255	0.219	8
He BS	2017	China	Asian	Gastric cancer	HB	MassARRAY	494/494	264	199	31	272	198	24	0.249	0.111	8
Sattarifard H	2017	Iran	Caucasian	Prostate cancer	HB	PCR-RFLP	178/180	150	28	0	139	41	0	0.114	0.085	7
Yang XB	2018	China	Asian	Gastric cancer	HB	MassARRAY	300/300	154	127	19	164	120	16	0.253	0.321	8
Zhou HC	2019	China	Asian	Colorectal cancer	HB	MassARRAY	50/50	26	18	6	27	19	4	0.270	0.799	8
rs1456315(A/G)								AA	AG	GG	AA	AG	GG			
Chung S	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1504/1553	905	495	104	663	703	187	0.347	0.975	6
Li L	2013	China	Asian	Colorectal cancer	HB	PCR-RFLP	313/595	167	119	27	294	262	39	0.286	0.055	7
Li L	2016	China	Asian	Gastric cancer	HB	PCR-RFLP	219/394	109	103	7	179	177	38	0.321	0.546	8
Sattarifard H	2017	Iran	Caucasian	Prostate cancer	HB	PCR-RFLP	178/180	30	148	0	92	88	0	0.244	0.000[a]	7

Table 1 (*contd*)

First author	Year	Country	Ethnicity	Tumour type	Source of control	Genotype method	Sample size (cases/control)	Genotyping distribution						MAF in control	HWE(P)	NOS
								Case			Control					
AlMutairi M rs13254738(A/C)	2019	Saudi Arabia	Caucasian	Colorectal cancer	HB	TaqMan	143/130	50 AA	57 AC	36 CC	61 AA	48 AC	21 CC	0.346	0.036[a]	7
Salinas CA	2008	USA	Caucasian	Prostate cancer	PB	SNPlex	1256/1234	571	535	150	581	543	110	0.309	0.289	8
Zheng SL	2010	China	Asian	Prostate cancer	PB	MassARRAY	277/152	176	92	9	71	70	11	0.303	0.262	8
Chung S rs7463708(T/G)	2011	Japan	Asian	Prostate cancer	HB	mPCR-RETINA	1504/1551	786 TT	579 TG	139 GG	609 TT	725 TG	217 GG	0.374	0.958	6
He BS	2017	China	Asian	Gastric cancer	HB	MassARRAY	494/494	241	209	44	228	209	57	0.327	0.390	8
Yang XB	2018	China	Asian	Gastric cancer	HB	MassARRAY	300/300	142	127	31	138	127	35	0.328	0.486	8
Zhou HC rs7841060(T/G)[b]	2019	China	Asian	Colorectal cancer	HB	MassARRAY	50/50	23 TT	21 TG	6 GG	22 TT	21 TG	7 GG	0.350	0.586	8
Sattarifard H	2017	Iran	Caucasian	Prostate cancer	HB	PCR-RFLP	178/180	29	149	0	96	84	0	0.233	0.000[a]	7
Hong JH	2019	Korea	Asian	Gastric cancer	HB	TaqMan	437/357	204	195	38ry>	169	159	29	0.304	0.319[b]	6

HWE, Hardy–Weinberg equilibrium; PB, population based; HB, hospital based; MAF, minor allele frequency; NOS, Newcastle–Ottawa Scale.
[a]Not included because the *P* of the HWE was < 0.05.
[b]Not included due to the limited number of studies for *PRNCR1* locus.

Discussion

Cancer has become a very large challenge for humans. However, its pathogenesis is not clear at present. Cumulative evidence suggests that cancer is a complex polygenic disease, and genetic factors play a vital role in its aetiology (Ponder 2001; Dong *et al.* 2008). LncRNAs potentially interact with DNA, RNA and protein molecules and play diverse regulatory functions, including chromatin remodelling, RNA splicing and editing, translational inhibition, mRNA destruction and epigenetic regulation of gene expression. Moreover, lncRNAs can function as either proto-oncogenes or anti-oncogenes in the development of cancer depending on the function of their target genes (Uszczynska-Ratajczak *et al.* 2018).

As a LncRNA, *PRNCR1* has been considered to be potentially linked to cancer risk, and its catalytic subunit has been extensively associated with the incidence of cancer (AlMutairi *et al.* 2019). *PRNCR1* mutations are reported to occur frequently in many types of cancer (AlMutairi *et al.* 2019). Several studies have explored the effect of *PRNCR1* SNPs on cancer susceptibility, including prostate cancer (Salinas *et al.* 2008; Zheng *et al.* 2010; Chung *et al.* 2011; Hui *et al.* 2014; Sattarifard *et al.* 2017), gastric cancer (Li *et al.* 2016; He *et al.* 2017; Yang *et al.* 2018; Hong *et al.* 2019), and colorectal cancer (Li *et al.* 2013; AlMutairi *et al.* 2019; Zhou *et al.* 2019), but the findings were inconsistent. For example, Li *et al.* (2013) previously found that there was a lack of relationship of rs16901946 with colorectal cancer risk. However, Zhou *et al.* (2019) found that rs16901946 was correlated with an increased risk of colorectal cancer. Hong *et al.* (2019) reported that rs13252298 was observed to increase the risk of gastric cancer in the Korean population; however, He *et al.* (2017) found no association between rs13252298 and gastric cancer risk in the Chinese population. The conclusions concerning the association of the *PRNCR1* SNPs with cancer susceptibility from previous studies were inconsistent, which might result from different cancer types, different ethnic populations, and limited sample sizes. Meta-analyses can be utilized for integrating data from multiple studies, hence increasing the size of the sample and the strength of the conclusions (Qin *et al.* 2016). Interestingly, we found three meta-analyses to examine whether *PRNCR1* SNPs can affect cancer susceptibility. However, the findings were conflicting rather than conclusive (table 4). For instance, Lv *et al.* (2017) performed the first meta-analysis of the relationship between five *PRNCR1* SNPs and cancer susceptibility in three articles. They found that only rs1016343 and rs16901946 were found to increase overall cancer risk, while rs1456315, rs13252298, and rs7007694 were not correlated with cancer risk. A study by Chu *et al.* (2017) including six studies showed that rs1016343 and rs16901946 were significantly associated with increased cancer risk, and no correlation of cancer risk was detected for rs1456315, rs13252298 and rs7007694.

Table 2. Meta-analysis results of the association between *PRNCR1* polymorphisms and cancer susceptibility.

				Allele model					Dominant model					Recessive model				
Variables	*n*	Case	Control	OR (95%CI)	P^a	I^2 (%)	P (Begg's)	P (Egger's)	OR (95%CI)	P^a	I^2(%)	P (Begg's)	P (Egger's)	OR (95%CI)	P^a	I^2(%)	P(Begg's)	P(Egger's)
rs1016343(C/T)																		
Overall	8	4434	4691	**1.19 (1.02–1.39)**	0.000	78.5	0.536	0.190	**1.25 (1.05–1.49)**	0.002	68.9	1.000	0.249	1.30 (0.95–1.78)	0.000	74.3	0.266	0.391
Cancer type																		
Prostate cancer	4	3323	3216	**1.42 (1.29–1.56)**	0.257	25.8			**1.47 (1.22–1.78)**	0.046	62.6			**1.83 (1.53–2.18)**	0.855	0.0		
Colorectal cancer	2	455	724	0.98 (0.81–1.17)	0.644	0.0			1.04 (0.81–1.33)	0.972	0.0			0.84 (0.57–1.23)	0.398	0.0		
Gastric cancer	2	656	751	0.96 (0.82–1.13)	0.443	0.0			1.00 (0.80–1.24)	0.977	0.0			0.85 (0.55–1.32)	0.196	40.2		
Ethnicity																		
Asians	6	3039	3329	1.17 (0.96–1.44)	0.000	83.9			1.24 (0.98–1.57)	0.001	76.7			1.23 (0.83–1.81)	0.000	80.6		
Caucasians	2	1395	1362	**1.33 (1.17–1.52)**	0.351	0.0			**1.35 (1.14–1.60)**	0.309	3.3			**1.70 (1.21–2.40)**	0.883	0.0		
rs13252298(A/G)																		
Overall	8	3298	3773	0.87 (0.73–1.04)	0.000	79.0	0.536	0.099	0.83 (0.65–1.06)	0.000	80.3	0.536	0.061	**0.78 (0.67–0.92)**	0.281	18.8	0.902	0.365
Cancer type																		
Colorectal cancer	3	507	768	**0.79 (0.66–0.94)**	0.957	0.0			**0.75 (0.59-0.94)**	0.779	0.0			0.73 (0.49–1.08)	0.679	0.0		
Gastric cancer	3	1013	1188	1.00 (0.77–1.30)	0.019	74.6			1.01 (0.69–1.46)	0.010	78.3			0.95 (0.71–1.25)	0.486	0.0		
Prostate cancer	2	1778	1817	0.79 (0.53–1.18)	0.005	87.5			0.69 (0.43–1.11)	0.009	85.4			**0.72 (0.58–0.89)**	0.047	74.6		
Ethnicity																		
Asians	7	3154	3650	0.87 (0.72–1.06)	0.000	81.9			0.83 (0.64–1.09)	0.000	82.9			0.79 (0.67–0.92)	0.210	28.6		
Caucasians	1	144	123	0.83 (0.57–1.20)	/	/			0.84 (0.52–1.37)	/	/			0.64 (0.28–1.48)	/	/		
rs16901946(A/G)																		
Overall	8	3461	3874	**1.17 (1.09–1.27)**	0.075	45.7	0.536	0.532	**1.20 (1.09–1.32)**	0.143	35.8	0.536	0.438	1.34 (0.90–2.00)	0.010	64.5	0.764	0.537
Cancer type																		
Gastric cancer	4	1450	1545	**1.17 (1.04–1.32)**	0.020	69.3			**1.29 (1.12–1.49)**	0.483	0.0			0.99 (0.43–2.26)	0.002	80.2		
Colorectal cancer	3	507	775	1.06 (0.86–1.30)	0.401	0.0			0.96 (0.74–1.24)	0.099	56.8			**1.75 (1.01–3.04)**	0.572	0.0		
Prostate cancer	1	1504	1554	1.21 (1.09–1.35)	/	/			1.20 (1.04–1.38)	/	/			1.51 (1.19–1.92)	/	/		
Ethnicity																		
Asians	7	3317	3744	**1.17 (1.09–1.26)**	0.049	52.5			**1.20 (1.09–1.32)**	0.099	43.8			1.34 (0.90–2.00)	0.01	64.5		
Caucasians	1	144	130	1.82 (0.33–10.00)	/	/			1.83 (0.33–10.1)	/	/			/	/	/		
rs7007694(T/C)																		
Overall	7	3051	3567	0.99 (0.85–1.15)	0.018	60.8	0.230	0.361	1.00 (0.91–1.11)	0.089	45.4	0.230	0.341	1.20 (0.99–1.43)	0.293	18.5	1.000	0.808
Cancer type																		
Gastric cancer	3	1013	1188	0.93 (0.67–1.28)	0.006	80.3			0.96 (0.81–1.13)	0.029	71.7			1.03 (0.70–1.50)	0.124	52.2		
Prostate cancer	2	1675	1734	0.90 (0.57–1.41)	0.070	69.6			1.02 (0.88–1.17)	0.072	69.2			1.19 (0.96–1.48)	/	/		
Colorectal cancer	2	363	645	1.15 (0.93–1.43)	0.979	0.0			1.09 (0.84–1.42)	0.990	0.0			1.70 (0.99–2.91)	0.899	0.0		

Table 2 (*contd*)

Variables	*n*	Case	Control	Allele model					Dominant model					Recessive model				
				OR (95%CI)	P^a	I^2 (%)	P (Begg's)	P (Egger's)	OR (95%CI)	P^a	I^2(%)	P (Begg's)	P (Egger's)	OR (95%CI)	P^a	I^2(%)	P(Begg's)	P(Egger's)
Ethnicity																		
Asians	6	2873	3387	1.02 (0.88–1.18)	0.031	59.2			1.02 (0.92–1.13)	0.158	37.3			1.18 (0.99–1.43)	0.293	18.5		
Caucasians	1	178	180	0.66 (0.40–1.10)	/	/			0.06 (0.37–1.08)	/	/			/	/	/		
rs1456315(A/G)																		
Overall	3	2036	2542	0.74 (0.53–1.04)	0.000	89.2	1.000	0.321	0.70(0.46–1.05)	0.000	88.5	1.000	0.150	0.64 (0.31–1.31)	0.002	84.2	1.000	0.908
Cancer type																		
Prostate cancer	1	1504	1553	0.57 (0.51–0.64)	/	/			0.49 (0.43–0.57)	/	/			0.54 (0.42–0.70)	/	/		
Colorectal cancer	1	313	595	0.95 (0.77–1.18)	/	/			0.85 (0.65–1.12)	/	/			1.35 (0.81–2.24)	/	/		
Gastric cancer	1	219	394	0.77 (0.59–1.00)	/	/			0.84 (0.60–1.17)	/	/			0.301 (0.14–0.71)	/	/		
Ethnicity																		
Asians	3	2036	2542	0.74 (0.53–1.04)	0.000	89.2			0.70 (0.46–1.05)	0.000	88.5			0.64 (0.31–1.31)	0.002	84.2		
rs13254738(A/C)																		
Overall	3	3037	2937	0.76 (0.51–1.15)	0.000	95.5	1.000	0.849	0.69 (0.43–1.11)	0.000	94.1	1.000	0.842	0.78 (0.40–1.52)	0.000	91.2	1.000	0.879
Cancer type																		
Prostate cancer	3	3037	2937	0.76 (0.51–1.15)	0.000	95.5			0.69 (0.43–1.11)	0.000	94.1			0.78 (0.40–1.52)	0.000	91.2		
Ethnicity																		
Asians	2	1781	1703	**0.66 (0.59–0.73)**	0.364	0.0			**0.58 (0.51–0.66)**	0.461	0.0			**0.61 (0.49–0.76)**	0.431	0.0		
Caucasians	1	1256	1234	1.11 (0.99–1.25)	/	/			1.07 (0.91–1.25)	/	/			1.39 (1.07–1.80)	/	/		
rs7463708(T/G)							1.000	0.779				1.000	0.796				1.000	0.729
Overall	3	884	884	0.91 (0.78–1.05)	0.927	0.0			0.92 (0.76–1.11)	0.969	0.0			0.80(0.59–1.09)	0.900	0.0		
Cancer type																		
Gastric cancer	2	794	794	0.91 (0.78–1.05)	0.697	0.0			0.92 (0.75–1.12)	0.802	0.0			0.80 (0.58–1.10)	0.652	0.0		
Colorectal cancer	1	50	50	0.91 (0.51–1.64)	/	/			0.92 (0.42–2.03)	/	/			0.84 (0.26–2.70)	/	/		
Ethnicity																		
Asians	3	884	884	0.91 (0.78–1.05)	0.927	0.0			0.92 (0.76–1.11)	0.969	0.0			0.80 (0.59–1.09)	0.900	0.0		

OR, odds ratio; CI, confidence interval

[a] *P* value for heterogeneity (a random-effects model was used when the *P* value for heterogeneity test was < 0.05; otherwise, a fixed-effect model was used). The results are in bold if $P < 0.05$.

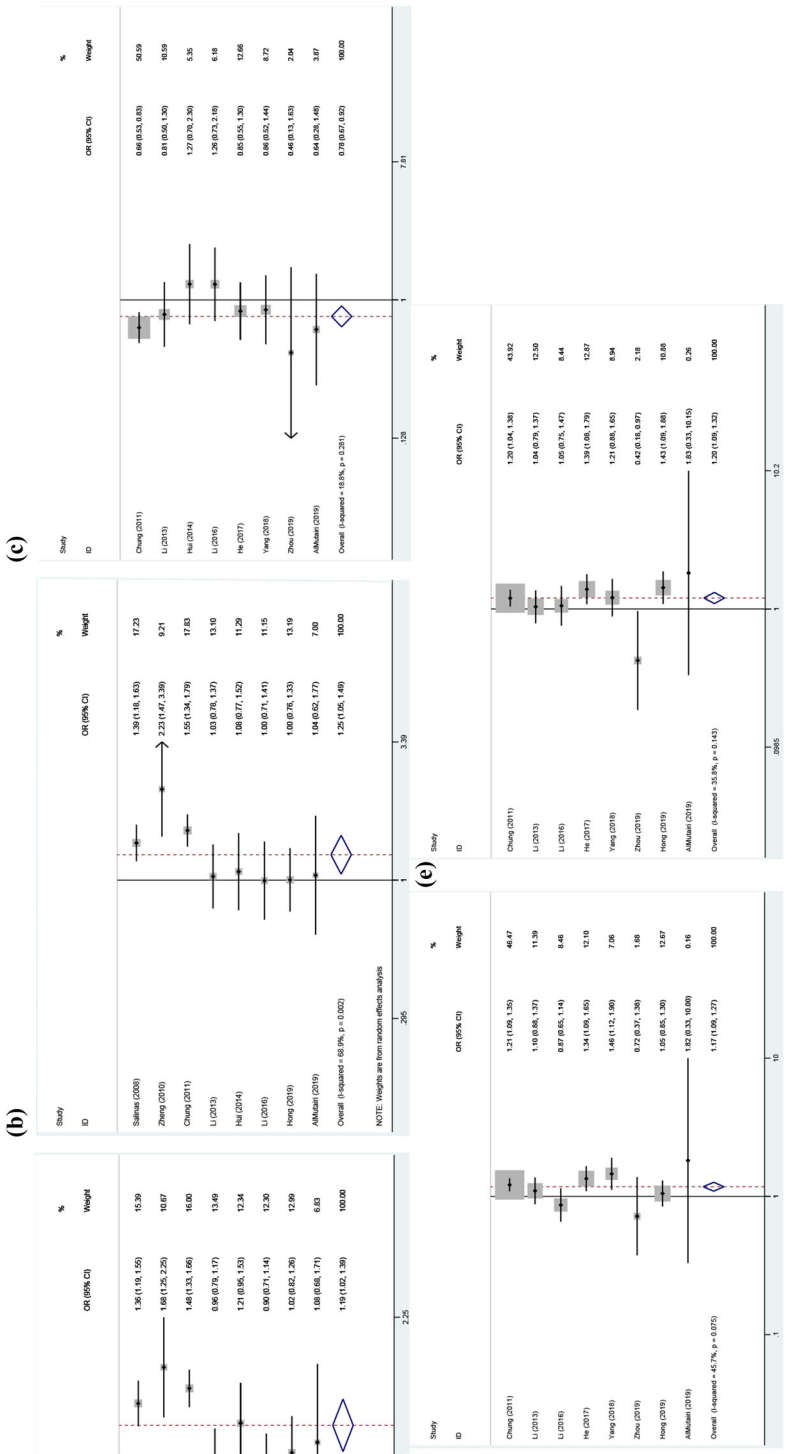

Figure 2. Forest plots of the association between *PRNCR1* polymorphisms and overall cancer risk under different models. (a) rs1016343 under allele model (T vs C). (b) rs1016343 under dominant model (TT+CT vs CC). (c) rs13252298 under recessive model (GG vs AG+AA). (d) rs16901946 under allele model (G vs A). (e) rs16901946 under dominant model (GG+AG vs AA).

Table 3. The results of ORs and 95% CIs of sensitivity analysis.

Excluding literature	Allelic model OR (95% CI)	Dominant model OR (95% CI)	Recessive model OR (95% CI)
rs1016343(C/T)			
Overall	1.19 (1.02–1.39)	1.25 (1.05–1.49)	1.04 (0.96–1.12)
Salinas *et al.* (2008)	**1.16 (0.96–1.41)**	**1.22 (0.98–1.52)**	1.24 (0.86–1.79)
Zheng *et al.* (2010)	**1.15 (0.98–1.35)**	1.19 (1.01–1.39)	1.26 (0.89–1.78)
Chung *et al.* (2011)	**1.14 (0.97–1.35)**	**1.19 (0.99–1.44)**	1.19 (0.87–1.65)
Li (2013)	1.24 (1.06–1.44)	1.29 (1.07–1.55)	**1.42 (1.05–1.92)**
Hui *et al.* (2014)	1.19 (1.01–1.42)	1.27 (1.06–1.54)	1.26 (0.87–1.80)
Li *et al.* (2016)	1.19 (1.01–1.42)	1.29 (1.08–1.54)	**1.44 (1.09–1.91)**
Hong *et al.* (2019)	1.22 (1.04–1.44)	1.29 (1.08–1.55)	1.34 (0.94–1.89)
AlMutairi *et al.* (2019)	1.20 (1.02–1.41)	1.27 (1.06–1.52)	1.29 (0.93–1.79)
rs13252298(A/G)			
Overall	0.87 (0.73–1.04)	0.83 (0.65–1.06)	0.78 (0.67–0.92)
Chung *et al.* (2011)	0.92 (0.80–1.06)	0.90 (0.74–1.09)	**0.91 (0.73–1.12)**
Li *et al.* (2013)	0.88 (0.72–1.09)	0.86 (0.64–1.14)	0.78 (0.66–0.92)
Hui *et al.* (2014)	0.85 (0.70–1.03)	0.82 (0.63–1.08)	0.78 (0.66–0.92)
Li *et al.* (2016)	**0.81 (0.70–0.93)**	**0.75 (0.62–0.90)**	0.75 (0.64–0.88)
He *et al.* (2017)	0.87 (0.71–1.08)	0.84 (0.63–1.12)	0.77 (0.65–0.91)
Yang *et al.* (2018)	0.86 (0.71–1.05)	0.83 (0.63–1.09)	0.77 (0.66–0.91)
Zhou *et al.* (2019)	0.88 (0.72–1.06)	0.83 (0.64–1.07)	0.79 (0.67–0.92)
AlMutairi *et al.* (2019)	0.87 (0.72–1.06)	0.83 (0.64–1.08)	0.79 (0.67–0.92)
rs16901946(A/G)			
Overall	1.17 (1.09–1.27)	1.20 (1.09–1.32)	1.34 (0.90–2.00)
Chung *et al.* (2011)	1.14 (1.03–1.26)	1.20 (1.06–1.36)	1.25 (0.71–2.22)
Li *et al.* (2013)	1.18 (1.09–1.28)	1.22 (1.11–1.35)	1.27 (0.79–2.05)
Li *et al.* (2016)	1.20 (1.11–1.30)	1.21 (1.10–1.34)	**1.49 (1.24–1.80)**
He *et al.* (2017)	1.15 (1.06–1.25)	1.17 (1.06–1.30)	1.25 (0.78–2.00)
Yang *et al.* (2018)	1.15 (1.07–1.25)	1.20 (1.09–1.32)	1.25 (0.80–1.95)
Zhou *et al.* (2019)	1.18 (1.10–1.27)	1.22 (1.11–1.34)	1.28 (0.84–1.95)
Hong *et al.* (2019)	1.19 (1.10–1.29)	1.17 (1.06–1.30)	1.43 (0.90–2.28)
AlMutairi *et al.* (2019)	1.17 (1.09–1.26)	1.20 (1.09–1.32)	1.34 (0.90–2.00)
rs7007694(T/C)			
Overall	0.99 (0.85–1.15)	1.00 (0.91–1.11)	1.20 (0.99–1.43)
Chung *et al.* (2011)	0.96 (0.77–1.18)	0.96 (0.84–1.11)	1.21 (0.87–1.65)
Li *et al.* (2013)	0.96 (0.80–1.14)	0.99 (0.89–1.10)	1.15 (0.96–1.39)
Li *et al.* (2016)	1.07 (0.99–1.16)	1.05 (0.94–1.16)	**1.25 (1.04–1.51)**
He *et al.* (2017)	0.96 (0.80–1.16)	0.99 (0.89–1.11)	1.18 (0.98–1.43)
Sattarifard *et al.* (2017)	1.02 (0.88–1.18)	1.02 (0.92–1.13)	1.20 (0.99–1.43)
Yang *et al.* (2018)	0.96 (0.80–1.15)	0.99 (0.89–1.10)	1.20 (0.99–1.44)
Zhou *et al.* (2019)	0.98 (0.83–1.15)	1.00 (0.91–1.11)	1.19 (0.99–1.43)
rs1456315(A/G)			
Overall	0.74 (0.53–1.04)	0.70 (0.46–1.05)	0.64 (0.31–1.31)
Chung *et al.* (2011)	0.87 (0.71–1.07)	0.85 (0.69–1.05)	0.67 (0.16–2.87)
Li *et al.* (2013)	**0.65 (0.49–0.86)**	0.63 (0.37–1.06)	**0.47 (0.29–0.76)**
Li *et al.* (2016)	0.73 (0.45–1.21)	0.64 (0.37–1.10)	0.83 (0.34–2.02)
rs13254738(A/C)			
Overall	0.76 (0.51–1.15)	0.69 (0.43–1.11)	0.78 (0.40–1.52)
Salinas *et al.* (2008)	**0.66 (0.59–0.73)**	**0.58 (0.51–0.66)**	**0.61 (0.49–0.76)**
Zheng *et al.* (2010)	0.86 (0.52–1.42)	0.79 (0.44–1.42)	0.93 (0.43–2.02)
Chung *et al.* (2011)	0.81 (0.42–1.56)	0.75 (0.36–1.56)	0.84 (0.27–2.61)
rs7463708(T/G)			
Overall	0.91 (0.78–1.05)	0.92 (0.76–1.11)	0.80 (0.59–1.09)
He *et al.* (2017)	0.94 (0.75–1.17)	0.94 (0.70–1.27)	0.87 (0.54–1.38)
Yang *et al.* (2018)	0.89 (0.74–1.06)	0.90 (0.71–1.14)	0.76 (0.51–1.12)
Zhou *et al.* (2019)	0.91 (0.78–1.05)	0.92 (0.75–1.12)	0.79 (0.58–1.10)

OR, odds ratio; CI, confidence interval.
The significant results are in bold.

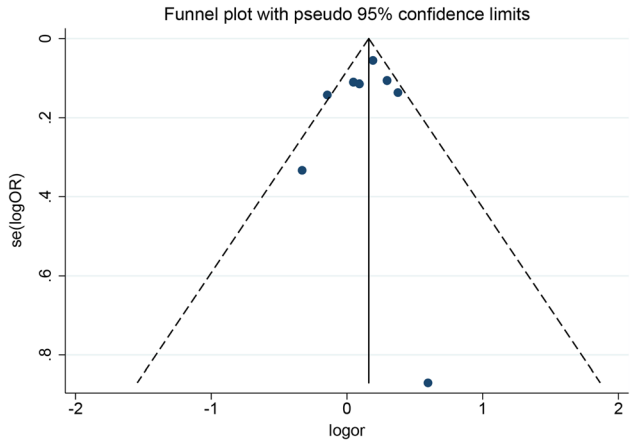

Figure 3. Begg's funnel plots of the association between *PRNCR1* rs16901946 polymorphism and cancer risk under allele model (G vs A).

Huang *et al.* (2018) conducted a meta-analysis on the correlation of five *PRNCR1* SNPs with cancer risk in seven studies, finding that rs16901946, rs13252298, rs1016343, and rs1456315 were correlated with cancer risk. No correlation with cancer risk was detected for rs7007694. Several new articles on this association have been published over the past two years. Thus, it is warranted to carry out this updated meta-analysis.

In the current study, we collected all relevant studies up to 10 April 2020, to comprehensively evaluate the cancer risk with the rs1016343, rs13252298, rs16901946, rs7007694, rs1456315, rs13254738 and rs7463708 polymorphisms in the *PRNCR1* gene. We reached to some new conclusions. For the rs1016343 C>T polymorphism, our data indicated that it was related to an increased risk of overall cancer risk and prostate cancer. These conclusions were in agreement with those in Huang *et al.* (2018). However, we also found that it increased the risk of cancer in Caucasians. For the rs13252298 A>G polymorphism, the same result as Huang *et al.*'s study showed that it reduced the overall risk of cancer (Huang *et al.* 2018). Further, we found that it reduced the risk of colorectal cancer. Concerning the rs16901946 A>G polymorphism, our study found a similar conclusion with Huang *et al.*'s study that it exhibited a correlation with an increased risk of overall cancer and gastric cancer risk (Huang *et al.* 2018). However, we found that it also increased the risk of colorectal cancer in Asians. For the rs1456315 A>G polymorphism, an association with decreased overall cancer risk was found in Huang *et al.*'s meta-analysis (Huang *et al.* 2018); however, in our study, there was no correlation between the rs1456315 A>G polymorphism and cancer risk. For the rs7007694 T>C polymorphism, there was no association with cancer risk, which was consistent with previous studies (Chu *et al.* 2017;

Table 4. List of results of published meta-analysis on the association lncRNA *PRNCR1* polymorphisms and cancer susceptibility.

First author	Year	Included articles (*n*)	Included SNPs (*n*)	SNPs	*n*	Sample size		Allele model OR (95%CI)	Dominant model OR (95%CI)	Recessive model OR (95%CI)
						Case	Control			
Lv Z	2017	3	5	rs1016343(C/T)	3	2034	2541	1.10 (0.77–1.56)	1.20 (0.87–1.66)	1.05 (0.51–2.15)
				rs13252298(A/G)	3	2033	2539	0.86 (0.59–1.27)	0.83 (0.48–1.41)	0.82 (0.57–1.17)
				rs16901946(A/G)	2	2036	2543	1.05 (0.76–1.45)	**1.18 (1.03–1.34)**	0.46 (0.04–6.00)
				rs7007694(T/C)	3	2029	2543	1.04 (0.80–1.35)	0.91 (0.53–1.58)	1.07 (0.82–1.41)
				rs1456315(A/G)	3	2036	2542	0.74 (0.53–1.04)	0.70 (0.46–1.05)	0.64 (0.31–1.31)
Chu H	2017	6	5	rs1016343(C/T)	6	3998	4284	**1.24 (1.04–1.47)**	**1.27 (1.04–1.53)**	**1.33 (0.92–1.92)**
				rs13252298(A/G)	4	2310	2806	0.89 (0.65–1.22)	0.84 (0.55–1.28)	0.89 (0.63–1.27)
				rs16901946(A/G)	3	2036	2543	1.09 (0.91–1.30)	**1.15 (1.02–1.29)**	0.92 (0.37–2.26)
				rs7007694(T/C)	3	2029	2543	0.96 (0.74–1.25)	0.93 (0.71–1.22)	1.10 (0.63–1.89)
				rs1456315(A/G)	3	2036	2542	0.74 (0.53–1.04)	0.70 (0.46–1.05)	0.64 (0.31–1.31)
Huang X	2018	7	5	rs1016343(C/T)	5	3571	3921	**1.31 (1.22–1.41)**	**1.41 (1.28–1.55)**	**1.42 (1.21–1.66)**
				rs13252298(A/G)	4	2527	3033	**0.78 (0.72–0.85)**	**0.81 (0.73–0.90)**	0.85 (0.72–1.01)
				rs16901946(A/G)	3	2217	2442	**1.15 (1.06–1.25)**	**1.17 (1.06–1.30)**	**1.21 (1.03–1.43)**
				rs7007694(T/C)	5	2701	3217	1.03 (0.95–1.12)	0.99 (0.89–1.10)	1.19 (0.98–1.44)
				rs1456315(A/G)	4	3290	3775	**0.77 (0.72–0.83)**	**0.72 (0.66–0.79)**	**0.69 (0.59–0.81)**
Current study	2020	12	7	rs1016343(C/T)	8	4434	4691	**1.19 (1.02–1.39)**	**1.25 (1.05–1.49)**	1.30 (0.95–1.78)
				rs13252298(A/G)	8	3298	3773	0.87 (0.73–1.04)	0.83 (0.65–1.06)	**0.78 (0.67–0.92)**
				rs16901946(A/G)	8	3461	3874	**1.17 (1.09–1.27)**	**1.20 (1.09–1.32)**	1.34 (0.90–2.00)
				rs7007694(T/C)	7	3051	3567	0.99 (0.85–1.15)	1.00 (0.91–1.11)	1.20 (0.99–1.43)
				rs1456315(A/G)	3	2036	2542	0.74 (0.53–1.04)	0.70 (0.46–1.05)	0.64 (0.31–1.31)
				rs13254738(A/C)	3	3037	2937	0.76 (0.51–1.15)	0.69 (0.43–1.11)	0.78 (0.40–1.52)
				rs7463708(T/G)	3	884	884	0.91 (0.78–1.05)	0.92 (0.76–1.11)	0.80 (0.59–1.09)

OR, odds ratio; CI, confidence interval.
$P < 0.05$ are in bold.

Lv *et al.* 2017; Huang *et al.* 2018). For the rs13254738 A>C polymorphism, our study was the first meta-analysis to explore its correlation with cancer risk. We found the rs13254738 A>C polymorphism reduced cancer risk in Asians. For the rs7463708 A>G polymorphism, our study was the first meta-analysis about cancer risk, and no correlation was discovered.

PRNCR1 is transcribed from the 'gene desert' region of chromosome 8q24. Chung *et al.* (2011), using resequencing, first confirmed that *PRNCR1* polymorphisms were related to prostate cancer susceptibility by affecting the activity of AR. *PRNCR1* binds to the C-terminus of the acetylated AR protein and then accelerates the association of the histone H3K79 methyltransferase DOT1L, leading to AR K349 methylation and recruiting lncRNA PCGEM1 to the DOT1L-mediated AR methylation N-terminus. Therefore, *PRNCR1* could act as a regulatory RNA to control gene expression (Yang *et al.* 2013). AR is a transcription factor involved in tumourigenesis that regulates the expression of downstream genes (Heemers and Tindall 2007). High expression of AR could promote the migration and invasion of gastric cancer cells, which might be related to the poor outcomes of gastric cancer patients (Tian *et al.* 2013). Subsequently, *PRNCR1* was found to play a role in the occurrence of gastric cancer. The mechanism by which the *PRNCR1* polymorphisms affect cancer risk is still not clearly understood. SNPs located in the *PRNCR1* gene may change the stability of the *PRNCR1* gene or the mRNA conformation and its interacting partners by affecting the predicted secondary structure of *PRNCR1* mRNA (Chung *et al.* 2011). This may be due to the unique structure of *PRNCR1*. The gene is mapped to the 'gene desert' region of chromosome 8q24, and its entire region has no introns, of which all polymorphisms are located in the exon region (Chung *et al.* 2011), which may affect the transcription and translation of the *PRNCR1* gene. However, more in-depth studies are required to elucidate the specific mechanisms.

Heterogeneities between studies were observed in almost all of the polymorphisms in this meta-analysis. The subjects stratified by cancer type and ethnicity found heterogeneity changes and decreases or even disappears in some subgroups, suggesting that ethnicity and cancer type might be important factors for heterogeneity. Moreover, many factors, such as research design, environmental factors, age and sex distribution, were also sources of heterogeneity. We also found that there are differences in MAF expression between different ethnicities for each *PRNCR1* SNP, indicating that there is heterogeneity between different races. For the rs16901946 C>T polymorphism, the value of MAF is 0.270 in Asian populations and 0.008 in Caucasian populations. This result was further confirmed based on HapMap data (International HapMap Project). The G allele frequency of the rs16901946 polymorphism is 0.295 in Asian populations (CHB+JPT) and 0.006 in European populations (CEU).

However, several limitations of this study should be acknowledged. First, our study included articles published only in English and Chinese, which may result in publication bias. Second, the total number of eligible studies and sample sizes were still relatively small to analyse the relationship of *PRNCR1* SNPs with cancer susceptibility. Therefore, statistical power might not be sufficient to discover weak but significant associations, especially in subgroup analyses. Third, all the data in this study were concentrated on Asians and Caucasians. It is not clear if these results can be promoted and applied in other populations. Finally, our assessment focussed on unadjusted results. Potential confounding factors, including age, lifestyle, drinking status, smoking status, and environmental factors, could not be extracted from all included studies, which might influence the final results.

Conclusion

In summary, our meta-analysis indicated that *PRNCR1* rs1016343 and rs16901946 were associated with increased cancer susceptibility; *PRNCR1* rs16901946 was related to decreased cancer susceptibility, and *PRNCR1* rs13254738 was linked to reduced cancer susceptibility in Asians. No significant associations were discovered between the *PRNCR1* rs7007694, rs1456315, and rs7463708 polymorphisms and cancer susceptibility. However, due to several limitations listed above, further larger studies are required to certify our findings.

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