RESEARCH ARTICLE

Pin1 Promoter rs2233678 and rs2233679 Polymorphisms in Cancer: A Meta-analysis

Yan-Mei Zhu[1,2], Jing-Wei Liu[1], Qian Xu[1], Yuan Yuan[1]*

Abstract

PIN1 is one member of the parvulin PPIase family. By controlling Pro-directed phosphorylation, PIN1 plays an important role in cell transformation and oncogenesis. There are many polymorphisms in the PIN1 gene, including rs2233678 and rs2233679 affecting the PIN1 promoter. Recently, a number of case-control studies were conducted to investigate the association between PIN1 gene rs2233678 and rs2233679 polymorphism and cancer risk. However, published data are still conflicting. In this paper, we summarized data for 5,427 cancer cases and 5,469 controls from 9 studies and attempted to assess the susceptibility of PIN1 gene polymorphism to cancers by a synthetic meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the relationship. All analyses were performed using Stata software. Our results suggested that rs2233678 represented a protective factor in overall analysis (CC vs GG: OR= 0.697, 95%CI: 0.498-0.976; CG vs GG: OR=0.701, 95%CI: 0.572-0.858; Dominant model: OR= 0.707, 95%CI: 0.590-0.847; C allele vs G allele: OR=0.734, 95%CI: 0.623-0.867) and especially for squamous cell carcinoma of the head and neck, lung cancer and breast cancer in Asians and Caucasians. The rs2233679 polymorphism was significantly associated with decreased cancer risk in overall analysis (CT vs CC: OR=0.893, 95%CI=0.812-0.981; Dominant model: OR=0.893, 95%CI=0.816-0.976; T allele vs C allele; OR=0.947, 95%CI=0.896-1.000) and especially in Asians. In conclusion, our meta-analysis suggested that -842G>C (rs2233678) and -667C>T (rs2233679) may contribute to genetic susceptibility for cancer risks. Further prospective research with larger numbers of worldwide participants is warranted to draw comprehensive and firm conclusions.

Keywords: PIN1 - single nucleotide polymorphism - cancer - susceptibility - meta-analysis

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Introduction

Cancer is a multi-step process resulting from complex interactions between genetic and environmental factors. Host genetic susceptibility plays an important role in developing cancer. Such various susceptibilities could be explained, in part, by single nucleotide polymorphisms (SNPs) of susceptible genes (Xue et al., 2010; Chung et al., 2011; Perez-Losada et al., 2011).

PIN1 (peptidylprolyl cis/trans isomerase, NIMA-interacting 1), which is one member of the parvulin peptidyl-prolyl isomerase (PPIases) families, is a 18 kDa protein containing a carboxy-terminal catalytic domain and a WW amino-terminal protein–protein interaction domain which can change conformation of phosphoproteins by recognizing and binding to specific phospho-Ser/Thr-Pro motifs (Lu et al., 2007; Liou et al., 2011; Theuerkorn et al., 2011). Its high expression was correlated with tumor progression and prognosis of patients in several types of cancer (Ayala et al., 2003; Miyashita et al., 2003; Fukuchi, et al., 2006; He et al., 2007). The PIN1 gene (NC_000019.8) spans over ~14 kb on chromosome 19p13, contains four exons, encodes a 163-amino acid protein, and has a promoter region of 1.5 kb. Two putative functional single nucleotide polymorphisms (SNPs) in the PIN1 promoter (rs2233678G>C: c.-842G>C [842nt upstream to initiation transcription code ATG] and rs2233679C>T: c.-667C>T) have been submitted to the PIN1 locus-specific database (www.LOVD.nl/PIN1). Dysregulation of PIN1 protein function and expression owing to SNPs in PIN1 promoter may alter the PIN1 signaling pathway, thereby modulate the risk of cancer.

Despite a series of molecular epidemiological studies aiming to examine the association between these two polymorphisms and the susceptibility of different cancer types, the available results remain conflicting. For the -842G>C polymorphism, Han et al. (2010) found that -842C variant alleles (GC+CC) were associated

*[1]Tumor Etiology and Screening Department of Cancer Institute and General Surgery, the First Affiliated Hospital of China Medical University, the Key Laboratory of Cancer Etiology and Prevention (China Medical University), Liaoning Provincial Education Department, [2]Department of Pathology, LiaoningCancer Hospital & Institute, Shenyang, Liaoning Province, China *For correspondence: yyuan@mail.cmu.edu.cn*

with decreased risk in breast cancer; Lu at al (Lu et al., 2013) found that -842CG heterozygote but not -842CC homozygote had a significantly decreased risk of nasopharyngeal carcinoma; In another two studies, -842G>C polymorphism had no influence on breast cancer (Naidu et al., 2011) and hepatocellular carcinoma risk (Segat et al., 2007). For -667C>T polymorphism, some studies found that -667T allele was associated with increased risk of nasopharyngeal carcinoma (Lu et al., 2013) and hepatocellular carcinoma (Segat et al., 2007), but others found that this polymorphism had no association with esophageal carcinoma (You et al., 2013), lung cancer (Lu et al., 2011), breast cancer (Han et al., 2010; Naidu et al., 2011) and squamous cell carcinoma of the head and neck (Lu et al., 2009). Therefore, it is highly necessary to perform a quantitative and systematic investigation with rigorous methods. To further evaluate the association between Pin1 polymorphisms (-842G>C, rs2233678 and -667C>T, rs2233679) and the risk of cancer, a meta-analysis was conducted on all eligible published studies in current study.

Materials and Methods

Identification and eligibility of relevant studies

The MEDLINE, EMBASE databases, Chinese National Knowledge Infrastructure (CNKI), Web of Science, and BIOSIS databases were used simultaneously using the following query: ('peptidylprolyl cis/trans isomerase, NIMA-interacting' or 'Pin1') and ('cancer' or 'tumor' or 'neoplasm' or 'malignancy' or 'carcinoma') and 'polymorphism' by two independent investigators (YM Zhu and JW Liu). Last search update was June 30, 2013. All published papers matching the eligible criteria were retrieved. Additional studies were identified by a manual search of references of original or review articles on this topic. Studies included in our meta-analysis have to meet the following criteria: (i) evaluated the relationship of the Pin1 polymorphisms Pin1-842G/C (rs2233678) or Pin1-667C/T (rs2233679) and cancer risk; (ii) in a case-control study design; (iii) contained available genotype frequency; (iv) excluded benign tumors, precancerous lesions. Major reasons for exclusion of studies were (i) only case population; (ii) the study did not have the outcomes of comparison reported or it was not possible to determine them; (iii) duplicate of previous publication.

Data extraction

Two of the authors (YM Zhu and JW Liu) extracted all data independently using a standardized extraction form and reached a consensus on all items. In the present study, the following information was extracted: first author, year of publication, country, ethnicity, cancer types, genotype frequencies for cases and controls, source of control groups (population- or hospital-based controls) and evidence of Hardy–Weinberg equilibrium (HWE). Meanwhile, we categorized larneal squamous cell carcinoma, nasopharyngeal carcinoma, esophageal carcinoma, squamous cell carcinoma of the head and neck into ' squamous cell carcinoma of the head and neck' for the stratified analysis.

Statistical analysis

Firstly, the strength of the association between the Pin1 polymorphisms (rs2233678 and (rs2233679) and cancer risk was measured by ORs with 95% confidence intervals (CIs). The statistical significance of the OR was determined using the Z test. Statistical heterogeneity between studies was assessed with the χ^2 -based Q test and I^2 (Higgins et al., 2003), heterogeneity was considered significant when $P<0.05$, and I^2 was used to qualify variation in OR attributable to heterogeneity. When heterogeneity was not an issue, fixed effect model with Mantel–Haenszel method was used (Ramsberg et al., 2012). Otherwise, a random effect model with Inverse variance method was used. Generally, we first evaluated the risks of the variant homozygote and heterozygote compared with the wild-type homozygote (CC vs GG and CG vs GG for rs2233678/TT vs CC and TC vs CC for 2233679). As to allele comparison, the risks of variant allele versus wild-type allele (C allele vs G allele for rs2233678/T allele vs C allele for 2233679) were estimated respectively. Then we evaluated the risks of the dominant and recessive effects of the variant allele (CC+CG vs GG and GG vs CG+GG for rs2233678/TT+TC vs CC and TT vs TC+CC for 2233679), respectively. In addition, we also performed stratification analyses on cancer type (divided into squamous cell carcinoma of the head and neck, lung cancer, breast cancer and hepatocellular carcinoma), ethnicity and source of control. We tested significance of deviation of genotype distribution at the polymorphic site from that expected from Hardy–Weinberg equilibrium (HWE) in the control sample for each of the selected case-control data sets. A χ^2 test was performed to examine HWE when genotype data was available. If HWE disequilibrium existed ($P<0.05$), or it was impossible to evaluate this equilibrium, sensitivity analysis was performed. Begg and Mazumdar (Begg et al., 1994) adjusted rank correlation test and the Egger regression asymmetry test (Egger, 1997) were utilized to provide a diagnosis of publication bias. All analyses were performed using Stata version 11.0 software (Stata,

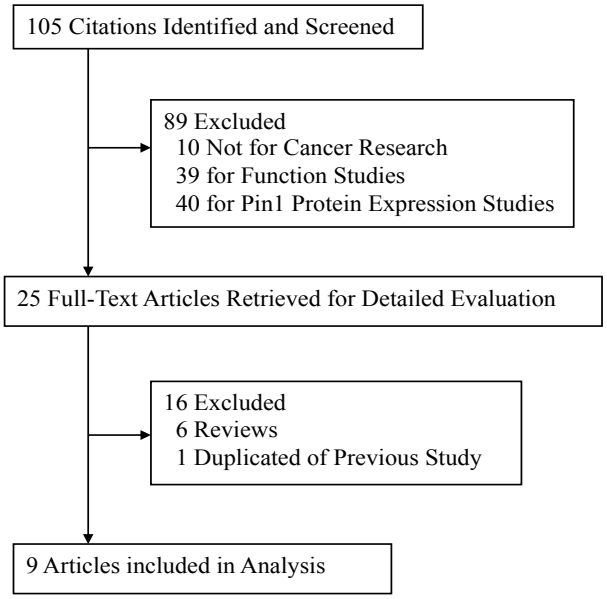

Figure 1. Studies Identified in This Meta-analysis Based on the Criteria for Inclusion and Exclusion

Table 1. Characteristics of Literature Included in This Meta-analysis for Pin1 -842G>C(rs2233678), -667C>T(rs2233679)

First author	Year	Country	Ethnicity	Cancer type	Language	Genotyping method	Source of control	Sample size		Case (-842G>C)			Control (-842G>C)			*P* of HWE	Case (-667T>C)			Control (-667T>C)			*P* of HWE
								Case	Control	CC	CG	GG	CC	CG	GG		CC	CT	TT	CC	CT	TT	
Yan Lu	2013	China	Asian	NC	English	PCR-RFLP	HB	178	156	21	22	135	8	38	110	0.06	61	81	36	56	84	16	0.06
Yonghe You	2013	China	Asian	EC	English	PCR-RFLP	HB	699	729	3	75	621	8	114	607	0.32	251	326	122	236	364	129	0.58
Wenping Cao	2012	China	Asian	LSCC	Chinese	PCR-RFLP	HB	95	100	0	8	87	3	23	74	0.47	38	31	26	32	45	23	0.35
Jiachun Lu	2011	China	Asian	LC	English	PCR-RFLP	PB	1559	1679	9	170	1380	12	271	1396	0.77	554	752	253	567	825	287	0.66
Rakesh Naidu	2011	Malaysia	Asian	BC	English	PCR-RFLP	HB	387	252	4	97	286	9	70	173	0.57	40	163	184	28	101	123	0.30
Chan H Han	2010	USA	Caucasian	BC	English	PCR-RFLP	HB	467	488	8	101	358	9	143	336	0.16	55	223	189	57	237	194	0.23
Jiachun Lu	2009	USA	Caucasian	SCCHN	English	PCR-RFLP	HB	1006	1007	9	159	838	11	202	794	0.64	105	474	427	96	468	443	0.08
Hongjun Zhao	2009	China	Asian	LC	Chinese	PCR-RFLP	PB	808	808	7	81	720	13	126	669	0.02	285	392	131	235	406	167	0.73
Ludovica Segat	2007	Italy	NA	HCC	English	NA	NA	228	250	2	59	167	7	40	203	0.01	22	95	111	32	113	105	0.85

NC, Nasopharyngeal carcinoma; EC, Esophageal carcinoma; LSCC, Larneal squamous cell carcinoma; LC, lung cancer; BC, breast cancer; SCCHN, Squamous cell carcinoma of the head and neck; HCC, hepatocellular carcinoma; NA, not available

Table 2. Association Between Pin1 -842G>C (rs2233678), -667C>T (rs2233679) with Cancer Risk

	Data set number	Fixed effect	Ramdon effect	Phet	I^2(%)
rs2233678					
CC vs GG	9	**0.70(0.50, 0.98)**	0.65(0.41, 1.04)	0.12	37.4%
CG vs GG	9	0.69(0.63, 0.77)	**0.70(0.57, 0.86)**	0.00	69.2%
CC+CG vs GG	9	0.70(0.63, 0.77)	**0.70(0.59, 0.85)**	0.00	64.0%
CC vs GG+GC	9	0.75(0.54, 1.05)	0.69(0.42, 1.13)	0.07	44.3%
C vs G	9	0.72(0.66, 0.79)	**0.73(0.62, 0.87)**	0.00	64.5%
rs2233679					
TT vs CC	9	0.90(0.80, 1.02)	0.94(0.79, 1.12)	0.07	44.1%
CT vs CC	9	**0.89(0.81, 0.98)**	0.89(0.81, 0.98)	0.73	0.0%
CT+TT vs CC	9	**0.89(0.82, 0.98)**	0.89(0.82, 0.98)	0.52	0.0%
TT vs CC+CT	9	0.97(0.89, 1.06)	1.00(0.87, 1.13)	0.07	45.2%
T vs C	9	**0.95(0.90, 1.00)**	0.96(0.89, 1.04)	0.10	40.6%

College Station, TX, USA). All statistical evaluations were made assuming a two-sided test with a significance level of 0.05, unless stated otherwise.

Results

Characteristics of studies

According to the searching strategy, 105 papers were found. We reviewed the titles, abstracts and the full texts of all retrieved articles through defined criteria. Finally, 9 studies including a total of 5427 cancer cases and 5469 controls were selected in our meta-analysis (Segat et al., 2007; Lu et al., 2009; Zhao, 2009; Han et al., 2010; Lu et al., 2011; Naidu et al., 2011; Cao, 2012; Lu et al., 2013; You et al., 2013) (Figure 1). The characteristics of the selected studies are listed in Table 1. The rs2233678 and rs2233679 polymorphisms were both investigated in 9 studies with the same cases and controls as mentioned above. The distribution of genotypes in the controls was consistent with the Hardy–Weinberg equilibrium for all selected studies, except for tow studies (Segat, et al., 2007; Zhao, 2009) for rs2233678 polymorphism.

Meta-analysis

The overall evaluation of the association between these two polymorphisms and cancer risk is presented in Table 2. For rs2233678 polymorphism, the overall analysis showed significant decreased risk in homozygous comparison (OR= 0.697, 95%CI: 0.498-0.976). This association was observed in heterozygous comparison (OR=0.701, 95%CI: 0.572-0.858), dominant model (OR=0.707, 95%CI: 0.590-0.847) and C allele compared to G allele (OR= 0.734, 95%CI: 0.623-0.867). Table 3 showed the results of stratified analysis for -842G>C rs2233678 polymorphism. In a stratified analysis by specific cancer type, we found decreased risk among studies of Squamous cell carcinoma of the head and neck (CG vs GG: OR=0.657, 95%CI: 0.553-0.780; Dominant model: OR=0.647, 95%CI: 0.492-0.850; C allele vs G allele: OR=0.691, 95%CI: 0.495-0.964), lung cancer (CG vs GG: OR=0.622, 95%CI=0.525-0.737; Dominant model (OR=0.622, 95%CI: 0.528-0.734; C allele vs G allele: OR=0.644, 95%CI=0.552-0.751), breast cancer (CG vs GG: OR=0.728, 95%CI=0.579-0.914; Dominant model: OR=0.711, 95%CI=0.570-0.888; C allele vs G allele: OR=0.732, 95%CI=0.601-0.892), whereas elevated risk was observed in hepatocellular carcinoma (CG vs GG: OR=1.793, 95%CI=1.143-2.814; Dominant model: OR=1.578, 95%CI=1.024-2.430). In the ethnicity subgroup analysis, significantly decreased cancer risks were found among Asians (CG vs GG: OR=0.629, 95%CI=0.552-0.718; Dominant model: OR=0.635, 95%CI=0.559-0.721; C allele vs G allele: OR=0.670, 95%CI=0.552-0.813) and Caucasians (CG vs GG: OR=0.713, 95%CI=0.595-0.855; Dominant model: OR=0.718, 95%CI=0.602-0.857; C allele vs G allele: OR=0.752, 95%CI=0.640-0.884). In a subgroup analysis by control characteristics, the ORs were significant in the heterozygote comparison, dominant and allele model for the hospital-based control (CG vs GG: OR=0.667, 95%CI =0.595-0.747; Dominant model: OR=0.674, 95%CI=0.604-0.753; C allele vs G allele: OR=0.711, 95%CI = 0.642-0.786). In one public-based study, the ORs were significant in the heterozygote comparison, dominant and allele model (CG vs GG: OR=0.597, 95%CI=0.443-0.805;

Dominant model: OR=0.588, 95%CI=0.441-0.784; C allele vs G allele: OR=0.602, 95%CI=0.461-0.785). As shown in Table 3, specific data for PIN1 -842G>C SNP was stratified, on the basis of sample size, into two subgroups: large sample (the total number of controls and cases not less than 500) and small-and-moderate sample (the total number of controls and cases less than 500) subgroups. Statistically significant finding was noted in large sample subgroup but not in small-and-moderate sample counterpart (CC vs GG: OR= 0.587, 95%CI=0.394-0.875; CG vs GG: OR=0.675, 95%CI =0.605-0.753; Dominant model: OR=0.669, 95%CI=0.601-0.744; Recessive model: OR=0.626, 95%CI=0.420-0.933; C allele vs G allele: OR=0.691, 95%CI= 0.626-0.762).

In the overall rs2233679 polymorphism analysis, the

Table 3. PIN1 -842G>C Pooled ORs and 95%CIs of stratified meta-analysis

Subgroups	Genotype	No.of Study	Test of association				Test of heterogeneity		
			OR(95%CI)	Z	*P* value	Model	X^2	*P* value	I^2(%)
SCCHN	CC vs GG	4	0.77(0.29, 2.05)	0.52	0.61	R	7.49	0.06	59.9%
	CG vs GG	4	**0.66(0.55, 0.78)**	4.79	0.00	F	5.73	0.13	47.6%
	CC+CG vs GG	4	**0.65(0.49, 0.85)**	3.12	0.00	R	6.02	0.11	50.2%
	CC vs GG+GC	4	0.84(0.31, 2.31)	0.34	0.74	R	8.10	0.04	63.0%
	C vs G	4	**0.69(0.50, 0.96)**	2.18	0.03	R	10.57	0.01	71.6%
LC	CC vs GG	2	0.62(0.33, 1.17)	1.48	0.14	F	0.41	0.52	0.0%
	CG vs GG	2	**0.62(0.53, 0.74)**	5.49	0.00	F	0.11	0.74	0.0%
	CC+CG vs GG	2	**0.62(0.53, 0.73)**	5.64	0.00	F	0.22	0.64	0.0%
	CC vs GG+GC	2	0.66(0.35, 1.24)	1.28	0.20	F	0.41	0.52	0.0%
	C vs G	2	**0.64(0.55, 0.75)**	5.59	0.00	F	0.37	0.54	0.0%
BC	CC vs GG	2	0.50(0.17, 1.51)	1.23	0.22	R	2.10	0.15	52.3%
	CG vs GG	2	**0.73(0.58, 0.91)**	2.74	0.01	F	0.97	0.32	0.0%
	CC+CG vs GG	2	**0.71(0.57, 0.89)**	3.01	0.00	F	0.36	0.55	0.0%
	CC vs GG+GC	2	0.54(0.17, 1.73)	1.04	0.30	R	2.33	0.13	57.1%
	C vs G	2	**0.73(0.60, 0.89)**	3.10	0.00	F	0.01	0.91	0.0%
HC	CC vs GG	1	0.35(0.07, 1.69)	1.31	0.19	F	0.00	NA	NA
	CG vs GG	1	**1.79(1.14, 2.81)**	2.54	0.01	F	0.00	NA	NA
	CC+CG vs GG	1	**1.58(1.02, 2.43)**	2.07	0.04	F	0.00	NA	NA
	CC vs GG+GC	1	0.31(0.06, 1.49)	1.46	0.14	F	0.00	NA	NA
	C vs G	1	1.32(0.90, 1.95)	1.42	0.16	F	0.00	NA	NA
Asian	CC vs GG	6	0.60(0.29, 1.23)	1.39	0.16	R	11.84	0.04	57.8%
	CG vs GG	6	**0.63(0.55, 0.72)**	6.88	0.00	F	6.45	0.27	22.5%
	CC+CG vs GG	6	**0.64(0.56, 0.72)**	6.99	0.00	F	6.21	0.29	19.5%
	CC vs GG+GC	6	0.65(0.31, 1.37)	1.14	0.25	R	12.91	0.02	61.3%
	C vs G	6	**0.67(0.55, 0.81)**	4.07	0.00	R	11.28	0.05	55.7%
Caucasian	CC vs GG	2	0.80(0.42, 1.54)	0.66	0.51	F	0.01	0.91	0.0%
	CG vs GG	2	**0.71(0.60, 0.86)**	3.66	0.00	F	0.38	0.54	0.0%
	CC+CG vs GG	2	**0.72(0.60, 0.86)**	3.67	0.00	F	0.32	0.57	0.0%
	CC vs GG+GC	2	0.87(0.45, 1.66)	0.43	0.67	F	0.04	0.85	0.0%
	C vs G	2	**0.75(0.64, 0.88)**	3.45	0.00	F	0.13	0.72	0.0%
HB	CC vs GG	8	0.77(0.53, 1.12)	1.35	0.18	F	11.20	0.08	46.4%
	CG vs GG	8	**0.67(0.60, 0.75)**	6.97	0.00	F	7.51	0.28	20.1%
	CC+CG vs GG	8	**0.67(0.60, 0.75)**	6.98	0.00	F	6.89	0.33	12.9%
	CC vs GG+GC	8	0.76(0.42, 1.38)	0.90	0.37	R	12.19	0.06	50.8%
	C vs G	8	**0.71(0.64, 0.79)**	6.61	0.00	F	11.29	0.08	46.8%
PB	CC vs GG	1	0.50(0.20, 1.26)	1.47	0.14	F	0.00	NA	NA
	CG vs GG	1	**0.60(0.44, 0.81)**	3.39	0.00	F	0.00	NA	NA
	CC+CG vs GG	1	**0.59(0.44, 0.78)**	3.62	0.00	F	0.00	NA	NA
	CC vs GG+GC	1	0.53(0.21, 1.35)	1.33	0.18	F	0.00	NA	NA
	C vs G	1	**0.60(0.46, 0.79)**	3.74	0.00	F	0.37	NA	NA
LS	CC vs GG	6	**0.59(0.39, 0.88)**	2.62	0.01	F	3.47	0.63	0.0%
	CG vs GG	6	**0.68(0.61, 0.75)**	7.05	0.00	F	3.21	0.67	0.0%
	CC+CG vs GG	6	**0.67(0.60, 0.74)**	7.39	0.00	F	2.75	0.74	0.0%
	CC vs GG+GC	6	**0.63(0.42, 0.93)**	2.30	0.02	F	3.66	0.60	0.0%
	C vs G	6	**0.69(0.63, 0.76)**	7.37	0.00	F	2.91	0.71	0.0%
SMS	CC vs GG	3	0.64(0.12, 3.48)	0.52	0.61	R	6.48	0.04	69.1%
	CG vs GG	3	0.66(0.22, 2.00)	0.74	0.46	R	20.13	0.00	90.1%
	CC+CG vs GG	3	0.73(0.30, 1.76)	0.71	0.48	R	14.94	0.00	86.6%
	CC vs GG+GC	3	0.65(0.10, 4.07)	0.46	0.65	R	7.59	0.02	73.6%
	C vs G	3	0.78(0.38, 1.61)	0.67	0.51	R	12.80	0.00	84.4%

OR, odds ratio; vs versus; R, random effect model; F, fixed effect model; SCCHN, Squamous cell carcinoma of the head and neck; LC, lung cancer; BC, breast cancer; HCC, hepatocellular carcinoma; PB, population-based; HB, hospital-based; LS, large sample; SMS, small and moderate sample; NA, not available

significant decreased risk was observed in heterozygous comparison (OR=0.893, 95%CI=0.812-0.981), dominant model (OR=0.893, 95%CI=0.816-0.976) and T allele vs C allele (OR=0.947, 95%CI=0.896-1.000). Table 4 showed the results of stratified analysis for -667C>T polymorphism. When evaluating the effect of the polymorphism by different tumor types, no association was found in any genetic models. We also performed sub-analysis stratified by ethnicity, we found that polymorphism decreased the cancer risk in Asians in the heterozygote comparison, dominant and allele model (CT vs CC: OR=0.875, 95%CI=0.789-0.972; Dominant model: OR=0.874, 95%CI=0.792-0.965; T vs C: OR=0.924, 95%CI=0.865-0.987); however, no association was found in Caucasians. The data were additionally stratified into hospital-based study and population-based study,

Table 4. PIN1 -667C>T Pooled ORs and 95%CIs of Stratified Meta-analysis

Subgroups	Genotype	No.of Study	Test of association				Test of heterogeneity		
			OR(95%CI)	Z	*P* value	Model	X^2	*P* value	I^2(%)
SCCHN	TT vs CC	4	0.96(0.79, 1.17)	0.43	0.67	F	5.25	0.15	42.9%
	CT vs CC	4	0.85(0.72, 1.01)	1.90	0.06	F	1.64	0.65	0.0%
	TT+CT vs CC	4	0.88(0.75, 1.03)	1.58	0.11	F	1.40	0.71	0.0%
	TT vs CC+CT	4	1.11(0.85, 1.47)	0.77	0.44	R	7.07	0.07	57.6%
	T vs C	4	0.96(0.88, 1.05)	0.84	0.40	F	3.48	0.32	13.7%
LC	TT vs CC	2	0.78(0.56, 1.07)	1.53	0.13	R	3.42	0.06	70.8%
	CT vs CC	2	0.89(0.78, 1.01)	1.88	0.06	F	1.33	0.25	24.9%
	TT+CT vs CC	2	0.85(0.69, 1.03)	1.63	0.10	R	2.52	0.11	60.3%
	TT vs CC+CT	2	0.85(0.67, 1.07)	1.40	0.16	R	2.16	0.14	53.7%
	T vs C	2	0.88(0.75, 1.03)	1.58	0.11	R	3.48	0.06	71.3%
BC	TT vs CC	2	1.02(0.74, 1.43)	0.14	0.89	F	0.01	0.92	0.0%
	CT vs CC	2	1.03(0.74, 1.43)	0.17	0.87	F	0.18	0.67	0.0%
	TT+CT vs CC	2	1.03(0.75, 1.40)	0.15	0.88	F	0.08	0.78	0.0%
	TT vs CC+CT	2	1.00(0.82, 1.22)	0.02	0.98	F	0.15	0.70	0.0%
	T vs C	2	1.00(0.87, 1.16)	0.06	0.96	F	0.03	0.87	0.0%
HCC	TT vs CC	1	1.54(0.84, 2.82)	1.39	0.16	F	0.00	NA	NA
	CT vs CC	1	1.22(0.67, 2.25)	0.65	0.52	F	0.00	NA	NA
	TT+CT vs CC	1	1.37(0.77, 2.44)	1.08	0.28	F	0.00	NA	NA
	TT vs CC+CT	1	1.31(0.91, 1.88)	1.47	0.14	F	0.00	NA	NA
	T vs C	1	1.25(0.95, 1.64)	1.61	0.11	F	0.00	NA	NA
Asian	TT vs CC	6	0.91(0.73, 1.15)	0.77	0.44	R	10.77	0.06	53.6%
	CT vs CC	6	**0.88(0.79, 0.97)**	2.50	0.01	F	3.84	0.57	0.0%
	TT+CT vs CC	6	**0.87(0.79, 0.97)**	2.67	0.01	F	4.58	0.47	0.0%
	TT vs CC+CT	6	0.98(0.81, 1.20)	0.16	0.87	R	11.29	0.05	55.7%
	T vs C	6	**0.92(0.87, 0.99)**	2.36	0.02	F	8.40	0.14	40.4%
Caucasian	TT vs CC	2	0.92(0.72, 1.18)	0.63	0.53	F	0.26	0.61	0.0%
	CT vs CC	2	0.94(0.74, 1.21)	0.47	0.64	F	0.04	0.84	0.0%
	TT+CT vs CC	2	0.93(0.74, 1.18)	0.57	0.57	F	0.13	0.72	0.0%
	TT vs CC+CT	2	0.97(0.84, 1.12)	0.45	0.65	F	0.34	0.56	0.0%
	T vs C	2	0.97(0.87, 1.08)	0.59	0.55	F	0.35	0.56	0.0%
HB	TT vs CC	8	0.95(0.83, 1.08)	1.70	0.09	F	5.69	0.46	0.0%
	CT vs CC	8	0.91(0.82, 1.01)	1.62	0.11	F	3.08	0.80	0.0%
	TT+CT vs CC	8	0.91(0.79, 1.05)	1.34	0.18	F	2.22	0.90	0.0%
	TT vs CC+CT	8	0.99(0.90, 1.09)	0.27	0.79	F	7.57	0.27	20.7%
	T vs C	8	0.96(0.91, 1.02)	1.20	0.23	F	3.92	0.69	0.0%
PB	TT vs CC	1	**0.65(0.49, 0.86)**	2.98	0.00	F	0.00	NA	NA
	CT vs CC	1	**0.80(0.64, 0.99)**	2.02	0.04	F	0.00	NA	NA
	TT+CT vs CC	1	**0.75(0.61, 0.93)**	2.66	0.01	F	0.00	NA	NA
	TT vs CC+CT	1	**0.74(0.58, 0.96)**	2.30	0.02	F	0.00	NA	NA
	T vs C	1	**0.81(0.7000.93)**	3.05	0.00	F	0.00	NA	NA
LS	TT vs CC	6	**0.86(0.76, 0.97)**	2.44	0.02	F	5.15	0.40	3.0%
	CT vs CC	6	**0.89(0.81, 0.99)**	2.21	0.03	F	2.54	0.77	0.0%
	TT+CT vs CC	6	**0.88(0.80, 0.97)**	2.66	0.01	F	3.69	0.60	0.0%
	TT vs CC+CT	6	0.93(0.84, 1.02)	1.61	0.11	F	3.83	0.57	0.0%
	T vs C	6	**0.93(0.87, 0.98)**	2.62	0.01	F	5.37	0.37	6.9%
SMS	TT vs CC	3	**1.48(1.01, 2.12)**	2.00	0.05	F	2.30	0.32	13.2%
	CT vs CC	3	0.88(0.63, 1.21)	0.81	0.42	F	2.68	0.26	25.3%
	TT+CT vs CC	3	1.03(0.76, 1.39)	0.19	0.85	F	2.59	0.27	22.8%
	TT vs CC+CT	3	**1.45(1.10, 1.92)**	2.61	0.01	F	2.21	0.33	9.6%
	T vs C	3	1.18(0.99, 1.42)	1.81	0.07	F	1.78	0.41	0.0%

OR, odds ratio; vs versus; R, random effect model; F, fixed effect model; SCCHN, Squamous cell carcinoma of the head and neck; LC, lung cancer; BC, breast cancer; HCC, hepatocellular carcinoma; PB, population-based; HB, hospital-based; LS, large sample; SMS, small and moderate sample; NA, not available

statistically significant finding was noted in one population -based study but not in hospital-based study. In terms of sample size, the results were contradictory between large sample subgroup and small-and-moderate subgroup. In large sample subgroup, significant decreased risk was observed in homozygous comparison (OR=0.858, 95%CI: 0.759-0.970), heterozygous comparison (OR=0.894, 95%CI: 0.810-0.987), dominant model (OR=0.881, 95%CI: 0.802-0.967) and T allele compared to C allele (OR= 0.926, 95%CI: 0.874-0.981); In small-and-moderate subgroup, significant increased risk was observed in homozygous comparison (OR=1.480, 95%CI: 1.008-2.172), and recessive model (OR=1.452, 95%CI: 1.097-1.923).

Table 5. The Results of Egger's Test for the Publication Bias

Comparison type	Begg's test		Egger's test	
	Z value	*P* value	t value	*P* value
for -842G>C(rs2233678)				
CC vs GG	-2.09	**0.04**	-2.33	**0.05**
CG vs GG	-0.63	0.53	-0.07	0.94
CC+CG vs GG	0.21	0.84	0.08	0.94
CC vs GG+GC	0.25	0.81	-0.75	0.48
C vs G	0.63	0.53	0.79	0.46
for -667C>T(rs2233679)				
TT vs CC	2.09	**0.04**	2.13	**0.07**
CT vs CC	0.63	0.53	0.22	0.83
TT+CT vs CC	1.25	0.21	1.05	0.33
TT vs CC+CT	-1.46	0.14	1.03	0.34
T vs C	0.00	1.00	-1.72	0.13

Sensitivity analyses and publication bias

Every one single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. This procedure did not change the pooled ORs supporting the robustness of our findings. Furthermore, when two studies that did not reach HWE in controls were excluded, the results were in agreement with the findings from foregoing analysis for all populations. Begg's and Egger's test were conducted to evaluate publication bias. These different test methods have come to the same conclusion. Both of them revealed statistical significance for publication bias in homozygous comparison models for -842G>C (rs2233678) and -667C>T (rs2233679). The results were shown in Table 5.

Discussion

It is well known that individual susceptibility plays important role in the development of most cancers. Polymorphisms of genes involved in carcinogenesis may have accounted for the susceptibility. Therefore, genetic susceptibility, especially single nucleotide polymorphism (SNP), to cancer has been a research focus in scientific community.

Many studies have been done to figure out the impact of Pin1 promoter SNPs on multiple types of cancer. The most intensively concerned ones are -842G>C (rs2233678) and -667C>T (rs2233679). However, the existing data were contradictory. To better understanding of the association between these polymorphisms and cancer risk, a meta-analysis with larger sample and subgroup analysis is necessary. The current study is the first meta-analysis associating Pin1 two promoter polymorphisms (-842G>C [rs2233678] and -667C>T [rs2233679]) with cancer risk.

Our study showed that -842C is a protect factor for cancer risk in total analysis. Considering the number of studies included in this article, we performed the stratified analyses by cancer types from different organs, by ethnicity and by control selection bias. Our results suggested that -842C tends to be a protective factor on squamous cell carcinoma of the head and neck, lung cancer and breast cancer. Contrary to other cancer types, in one hepatocellular carcinoma study, the variant -842C allele is associated with increased cancer risk, contrary to others. The reason may be that the -842G>C (rs2233678) polymorphism may have different effect on carcinogenesis in different organs, reflecting the diversities of the susceptible factors for different tumor types. In addition, this observed different effect could be likely due to chance because it is a small sample size with only 228 cases and 250 controls may have generated a fluctuated risk estimate or may have insufficient statistical power to detect a slight effect. So studies with larger sample size in hepatocellular carcinoma are necessary to fully understand the relationship between the polymorphism and the risk of hepatocellular carcinoma. -842C is also a protect factor both in Asian and Caucasian. When stratifying the source of control, significant associations were observed in hospital-based and population-based controls. This may result from most of the included studies matching age, sex and residential area to control selection bias. In stratified analysis by sample size, -842C is a protect factor in large sample size subgroup but not in small-and-moderate subgroup, which may due to insufficient statistical power for small size study.

Previous functional analyses of the PIN1 -842G>C polymorphism found that -842C variant allele had a lower transcription activity in luciferase assay which indicated that PIN1 gene expression driven by the variant -842C allele was much lower than those driven by the -842G allele (Lu et al., 2009; Lu et al., 2011). Furthermore, the deficiency in binding of nuclear protein by the -842C allele probe was also observed compared to the -842G allele probe in electrophoretic mobility shift assay (EMSA). All of above indicated that -842 C variant genotypes might decreased PIN1 protein expression, lead to reduced oncogenic phosphorylation signals and thus reduce the cancer risk.

Our meta-analysis results showed that -667C>T polymorphism decreased cancer risk in total analysis. When stratified analysis by cancer type, no association was found in any cancer type. In the stratified analyses by ethnicity, significantly decreased cancer risks were found for -667C>T among Asians but not in Caucasians. Different ethnicities may have different genetic backgrounds, which influence the association between polymorphism and cancer susceptibility. Inconsistency between the two ethnicities can be explained by the possibility that different ethnic groups live with multiple life styles and environmental factors and thus yield diverse gene-environment interactions (Molina et al., 2009; Dick, 2011; Carpenter et al., 2013). And different populations carry different genotype and/or allele frequencies of this locus polymorphism: the rs2233679 C allele among controls between Asian (0.445) and Caucasian (0.662) is highly significantly different, and it may lead to various degrees of cancer susceptibility (Gao et al., 2010; De et al., 2012; Euhus et al., 2013). When stratified analysis by sample size, the results was inconsistent between two subgroups. In large sample subgroup, -667T allele is a protect factor, which is opposite to that in small-and-moderate sample subgroup. This difference may be caused by the small sample size. There are only 3 studies in small-and-moderate sample subgroup, the total case number is 501

and control number is 506. Compared with large sample size, small sample size may have limited statistical power to result a real risk estimate. Furthermore, functional study should be performed to validate these results.

Despite our efforts in performing a comprehensive analysis, some limitations exist in our meta-analysis. First, we pooled the data using unadjusted information, whereas a more precise analysis could to be conducted if detailed information of original data is available. Second, a lack of original data of the reviewed studies limited our further evaluation of potential interactions, including the interactions between different genes and between gene and environment factors. Third, only English and Chinese documents were included in this meta analysis, while reports that were written in other languages and other unpublished data or ongoing studies were not available, which may cause certain publication bias in our meta-analysis. The last but not the least, the pooled sample size was relatively limited in this meta-analysis. Therefore, this meta-analysis could only preliminarily appraise the association of rs2233678, rs2233679 polymorphisms with currently-reported cancers. More studies are still required to get a more reliable result.

In conclusion, our meta-analysis suggested that the -842G>C (rs2233678) polymorphism may contribute to genetic susceptibility for overall cancers risks especially in squamous cell carcinoma of the head and neck, lung cancer and breast cancer, as well as in Asian and Caucasian. The -667C>T (rs2233679) polymorphism might be associated with genetic susceptibility for overall cancers risks especially in Asian. Future well-designed and larger population studies are of great value to confirm these findings. Moreover, combination of genetic factors together with environmental exposures should also be considered.

In conclusion, -842G>C (rs2233678) and -667C>T (rs2233679) may contribute to genetic susceptibility for cancers risks.

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