RESEARCH ARTICLE

Association between the *HSPA1B* ±1267A/G Polymorphism and Cancer Risk: a Meta-analysis of 14 Case-Control Studies

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Abstract

Background: Previous epidemiological studies have suggested a potential role of the *HSPA1B*±1267A/G polymorphism in risk of developing cancer. However, the results were inconsistent. Therefore, we performed this meta-analysis to summarize the possible association with cancer risk. Materials and Methods: We retrieved relevant articles from PubMed, EMBASE, ISI Web of Science, Chinese Biomedical Literature and Chinese National Knowledge Infrastructure. Studies were selected using specific criteria. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess those associations. All analyses were performed using STATA software. Results: Fourteen case-control studies, including 1, 834 cancer cases and 2, 028 controls were included in this meta-analysis. Overall, the results indicated that the G allele of *HSPA1B* gene ±1267A/G was significantly associated with an increased cancer risk in all genetic models (G *vs* A: OR=1.51, 95%CI 1.17-1.95, *p*=0.001; GG *vs* AA: OR=2.93, 95%CI 1.50-5.74, *p*=0.002; AG *vs* AA: OR=1.48, 95%CI 1.10-1.98, *p*=0.009; GG/AG *vs* AA: OR=1.69, 95%CI 1.22-2.33, *p*=0.001; GG *vs* AG/AA: OR=2.31, 95%CI 1.24-4.32, *p*=0.009). In the subgroup analysis stratified by ethnicity, a significant association was identified in Caucasians (G *vs* A: OR=1.35, 95%CI 1.08-1.69, *p*=0.008; GG/AG *vs* AA: OR=1.36, 95%CI 1.09-1.70, *p*=0.007), but not in Asians. In the stratified analysis by cancer types, individuals with the G allele showed an increased risk of hepatocellular carcinoma compared with carriers of the A allele (OR=2.40, 95%CI 1.47-3.91, *p*< 0.001). Inversely, individuals with the GG genotype showed a decreased risk of gastric cancer compared with carriers of the AG/GG genotypes (GG *vs* AG/AA: OR=0.39, 95%CI 0.20-0.70, *p*=0.007). Conclusions: This meta-analysis suggests associations between the *HSPA1B* ±1267A/G polymorphism and risk of cancer. However, this association might be Caucasian-specific and the G allele of this polymorphism probably increases risk of hepatocellular carcinoma while decreasing risk of gastric cancer. Further well-designed studies based on larger sample sizes are needed to validate these findings.

Keywords: Heat-shock proteins (HSPs) - cancer risk - polymorphism - meta-analysis

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Introduction

Heat-shock proteins (HSPs), known as evolutionarily highly conserved stress-inducible proteins, play an important role in regulating cellular homeostasis by means of refolding of damaged proteins and inhibiting accumulation of protein aggregates (Georgopoulos and Welch, 1993; Becker and Craig, 1994; Hartl and Hayer-Hartl, 2002). Heat shock protein 70 (HSP70), one of the most well-known HSPs, function as key components not only in cellular homeostasis, but also in upregulation of pro-inflammatory cytokines and antigen processing and presentation (DeNagel and Pierce, 1992; Asea et al., 2000). It has been demonstrated that HSP70 expression is abnormally high in cancer cells and it may be involved in oncogenesis and protecting malignant cells against host immunologic reactions (Radons and Multhoff, 2005; Calderwood et al., 2006; Garrido et al., 2006). Thus, HSP70 plays a critical role in tumor promotion, treatment and prognosis (Ciocca et al., 1993; Ciocca and Calderwood, 2005; Anand et al., 2011; Khalil et al., 2011; Cai et al., 2013; Wang et al., 2014).

HSPA1B, encodes HSP70-2 which is a component of HSP70, is located in the class III region of the human major histocompatibility complex (MHC) on chromosome 6p21.3 (Milner and Campbell, 1992). Published genome-wide association studies in Caucasians have reported that several polymorphisms were associated with cancer risk in this region (Hung et al., 2008; Wang et al., 2008; Broderick et al., 2009), and the *HSPA1B* ±1267A/G polymorphism

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justly located in this region was most widely studied. It has reported that the *HSPA1B* ±1267A/G variant can regulate the expression of HSP70-2 by interfering with the secondary structure and stability of mRNA (Schroeder et al., 1999; Wu et al., 2004), thus may affect its anti-apoptotic and immune modulator function, therefore, resulting in predisposition to and prognosis of cancers.

A number of epidemiological studies have examined the association between this ±1267A/G polymorphism and cancer risk (Chouchane et al., 1997; Mestiri et al., 2001; Jalbout et al., 2003; Toth et al., 2007; Jeng et al., 2008; Rehman et al., 2009; Shibata et al., 2009; Li et al., 2010; Wang et al., 2010; Srivastava et al., 2012; Zagouri et al., 2012; Ferrer-Ferrer et al., 2013; Medhi et al., 2013). However, the results were inconclusive or even contradictory which may be due to small sample size, different ethnic populations and cancer types in the corresponding studies. Therefore, we performed a meta-analysis followed by stratified analysis of all eligible studies to systematically clarify the association between the *HSPA1B* ±1267A/G polymorphism and cancer risk.

Materials and Methods

Literature Search

A comprehensive search of five electronic databases, including PubMed, EMBASE, ISI Web of Science, Chinese Biomedical Literature (CBM) and Chinese National Knowledge Infrastructure (CNKI), for all studies published through December 31, 2013, that had examined the association between *HSPA1B* ±1267 polymorphism and cancer risk. The following search terms and their synonyms were used: "heat shock protein70 or hsp70 or HSPA1B", "gene or polymorphism or allele or variation", "cancer or carcinoma or neoplasm or tumor". References lists in retrieved articles were also screened. We included published articles on relevant studies carried out in human subjects in all languages.

Inclusion and Exclusion Criteria

Eligible studies for further meta-analysis had to meet all of the following criteria: (1) case-control study design; (2) investigating the association between ±1267A/G polymorphism and cancer risk; (3) describing detail genotype frequencies in case and control groups so that an odds ratio (OR) with 95% confidence interval (CI) could be calculated. The major exclusion criteria were: (1) duplicate of previous publication; (2) abstract, review, comment and editorial; (3) animal studies; (4) family or sibling pairs based studies; (5) sufficient original genotype frequencies were unavailable, even contacting the corresponding author of the relevant articles. If there was more than one study published by the same investigators using the same or overlapping data, we selected the article involving complete design and larger sample size.

Data extraction

Two reviewers (Kuang and Yu) independently extracted the following information from the eligible studies: first author's surname, year of publication, country of origin, ethnicity, source of control, cancer type, genotyping method, sample size of genotyped cases and controls, genotype frequencies in case and control groups. If the study involving more than one type of cancer, data were extracted separately as independent studies. Any disagreements on the data extracted by the two reviewers were resolved by discussion until reaching conformity on all items among all authors.

Statistical analysis

Firstly, we assessed the genotype frequencies of ±1267A/G polymorphism for HWE in control groups by Chi-square test and a $p<0.05$ was considered as significant disequilibrium (Schaid and Jacobsen, 1999). The strength of the association between ±1267A/G polymorphism and cancer risk was calculated by OR with its 95%CI. The pooled ORs and their 95%CI in each comparison were performed for allelic comparison (G *vs* A), homozygote model (GG *vs* AA), heterozygote model (AG *vs* AA), dominant model (GG/AG *vs* AA) and recessive model (GG *vs* AG/AA), respectively. The Z test was conducted to determine the significance of the pooled ORs. As there were multiple comparisons, bonferroni correction was used to adjust the significance alpha level, and $p<0.01$ was considered statistically significant. The chi-square based Cochran's Q test and I^2 statistics were employed to assess the between-study heterogeneity and heterogeneity was considered to be significant when $p<0.10$ in Q test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). The fixed-effects model (based on Mantel-Haenszel method) was applied to calculate the pooled ORs when the P value for Q statistic was larger than 0.10; otherwise, the random-effects model (based on DerSimoniane-Laird method) was used (DerSimonian and LairdN, 1986). Secondly, in order to explore the source of heterogeneity, we performed sub-group analyses as well as meta-regression among variables, including ethnicity (Caucasian and Asian), cancer types (if one cancer type contained less than two individual studies, it was combined into other cancer subgroups), source of control (population-based and hospital-based) and HWE, respectively (Higgins and Thompson, 2004). Thirdly, we carried out sensitivity analysis to evaluate the influence of each study on the overall estimate by sequentially removing individual study. Finally, we conducted Funnel plot and Egger's linear regression test to examine potential publication bias, and $p<0.05$ was considered to be statistically significant publication bias (Begg and Mazumdar, 1994; Egger et al., 1997; Peters et al., 2006). All P values were two sided, and all statistical analyses were conducted by using STATA statistical software (version 11.0; StataCorp, College Station, Texas USA).

Results

Characteristics of eligible studies

The flow chart in Figure 1 displayed the comprehensive literature search and study selection procedures for *HSPA1B* ±1267A/G polymorphism and cancer risk. After careful search and selection, 13 eligible publications were identified according to inclusion criteria. Besides, the publication reported by Chouchane et al. applied two

different cancer groups (non-Hodgkin's lymphoma and breast cancer) with the same set of control, which was considered as two case-control studies. Finally, a total of 14 case-control studies with 1, 834 cases and 2, 028 controls were enrolled in our meta-analysis. The main characteristics of each study were summarized in Table 1. Among the 14 applicable studies, 7 of them were carried out in Asian populations and 7 in Caucasian populations. In view of control source, 12 studies were population-based, 1 study was hospital-based, and 1 study was not

Table 1. Characteristics of the Eligible Studies in the Meta-analysis

Study	year	Country	Ethnicity	Cancer type	Control source	No. of case/control	Case AA	Case AG	Case GG	Control AA	Control AG	Control GG	HWE
Maura	2013	Costa Rica	Caucasian	Gastric	PB	39/79	6	26	7	17	32	30	Y
Medhi	2013	India	Asian	Hepatocellular	Not described	185/200	111	59	15	156	40	4	Y
Zagouri	2012	Greece	Caucasian	Breast	PB	113/124	24	82	7	32	76	16	N
Srivastava	2012	India	Asian	Pancreatic	PB	50/50	13	29	8	33	15	2	Y
Wang	2010	China	Asian	Lung	PB	159/202	57	72	30	56	100	46	Y
Rehman	2009	India	Asian	Skin	PB	118/95	10	103	5	24	70	1	N
Jeng	2008	China	Asian	Hepatocellular	PB	150/150	28	55	67	70	65	15	Y
Toth	2007	Hungary	Caucasian	Colorectal	PB	183/141	69	87	27	65	57	19	Y
Jalbout	2003	Tunisia	Caucasian	Nasopharyngeal	PB	140/274	40	68	32	101	138	35	Y
Mestiri	2001	Tunisia	Caucasian	Breast	PB	243/174	52	123	68	35	130	9	N
Chouchane	1997	Tunisia	Caucasian	non-Hodgkin's	PB	44/106	4	28	12	22	82	2	N
Chouchane	1997	Tunisia	Caucasian	Breast	PB	40/106	4	26	10	22	82	2	N
Li	2010	China	Asian	Hepatocellular	PB	145/127	48	71	26	56	62	9	Y
Shibata	2009	Japan	Asian	Gastric	HB	223/200	46	173	6	33	155	12	N

*PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium

Table 2. Meta-analysis of the Association Between the Hspa1b +1267A/G Polymorphism and Cancer Risk in All Genetic Models

Comparisons		N	Test of association			Test of heterogeneity	
			OR (95%CI)	*P* value	Model	*P* value	I^2 (%)
Overall	G *vs* A	14	1.51 (1.17-1.95)	0.001	R	< 0.001	85.2
	GG *vs* AA	14	2.93 (1.50-5.74)	0.002	R	< 0.001	85.2
	AG *vs* AA	14	1.48 (1.10-1.98)	0.009	R	< 0.001	68.3
	GG/AG *vs* AA	14	1.69 (1.22-2.33)	0.001	R	< 0.001	76.1
	GG *vs* AG/AA	14	2.31 (1.24-4.32)	0.009	R	< 0.001	86.5
Overall for HWE	G *vs* A	8	1.62 (1.09-2.40)	0.017	R	< 0.001	89.2
	GG *vs* AA	8	2.55 (1.18-5.51)	0.018	R	< 0.001	85.7
	AG *vs* AA	8	1.60 (1.13-2.26)	0.008	R	0.004	66.6
	GG/AG *vs* AA	8	1.83 (1.20-2.80)	0.005	R	< 0.001	80.3
	GG *vs* AG/AA	8	0.52 (0.26-1.03)	0.062	R	< 0.001	85.4
Ethnicity							
Asian	G *vs* A	7	1.70 (1.06--2.73)	0.026	R	< 0.001	91.8
	GG *vs* AA	7	3.12 (0.99-9.77)	0.051	R	< 0.001	89.4
	AG *vs* AA	7	1.67 (1.03-2.71)	0.037	R	< 0.001	80.1
	GG/AG *vs* AA	7	1.96 (1.10-3.51)	0.023	R	< 0.001	87.4
	GG *vs* AG/AA	7	2.31 (1.24-4.32)	0.069	R	< 0.001	85.8
Caucasian	G *vs* A	7	1.35 (1.08-1.69)	0.008	R	0.026	58.2
	GG *vs* AA	7	2.76 (1.18-6.49)	0.020	R	< 0.001	81.0
	AG *vs* AA	7	1.21 (0.96-1.52)	0.110	F	0.140	37.8
	GG/AG *vs* AA	7	1.36 (1.09-1.70)	0.007	F	0.562	0.0
	GG *vs* AG/AA	7	2.33 (0.89-6.10)	0.084	R	< 0.001	88.8
Cancer type							
Gastric	G *vs* A	2	0.84 (0.66-1.07)	0.159	F	0.671	0.0
	GG *vs* AA	2	0.46 (0.21-1.04)	0.061	F	0.466	0.0
	AG *vs* AA	2	1.21 (0.44-3.35)	0.704	R	0.078	67.8
	GG/AG *vs* AA	2	0.88 (0.57-1.36)	0.564	F	0.245	26.1
	GG *vs* AG/AA	2	0.39 (0.20-0.77)	0.007	F	0.793	0.0
Hepatocellular	G *vs* A	3	2.40 (1.47-3.91)	< 0.001	R	0.004	82.1
	GG *vs* AA	3	6.07 (2.80-13.19)	< 0.001	R	0.098	57.0
	AG *vs* AA	3	1.80 (1.34-2.42)	< 0.001	F	0.377	0.0
	GG/AG *vs* AA	3	2.41 (1.51-3.87)	< 0.001	R	0.058	64.8
	GG *vs* AG/AA	3	4.98 (3.18-7.79)	< 0.001	F	0.191	39.6
Breast	G *vs* A	3	1.40 (0.95-2.06)	0.091	R	0.042	68.5
	GG *vs* AA	3	3.86 (0.56-26.43)	0.169	R	< 0.001	88.0
	AG *vs* AA	3	1.06 (0.55-2.05)	0.859	R	0.070	62.5
	GG/AG *vs* AA	3	1.16 (0.81-1.64)	0.418	F	0.291	18.9
	GG *vs* AG/AA	3	3.62 (0.43-30.28)	0.236	R	< 0.001	92.4
Others	G *vs* A	6	1.49 (1.06-2.11)	0.024	R	< 0.001	80.2
	GG *vs* AA	6	3.15 (1.21-8.16)	0.018	R	< 0.001	82.9
	AG *vs* AA	6	1.71 (1.00-2.92)	0.049	R	0.001	76.3
	GG/AG *vs* AA	6	1.88 (1.06-3.31)	0.030	R	< 0.001	81.0
	GG *vs* AG/AA	6	2.20 (1.05-4.61)	0.038	R	0.001	76.6

*[a]data after excluding those studies' controls not in Hardy-Weinberg equilibrium; [b]number of sutdies; R: random-effects model; F: fixed-effects model

Table 3. Egger's Linear Regression Test to Measure the Funnel Plot Asymmetric

Groups	Egger's test: t value (*P* value)				
	G vs A	GG vs AA	AG vs AA	GG/AG vs AA	GG vs AG/AA
Overall	1.30 (0.219)	1.31 (0.216)	2.09 (0.059)	1.57 (0.143)	0.86 (0.409)
Overall for HWE	0.58 (0.580)	0.79 (0.459)	1.73 (0.134)	1.01 (0.349)	0.44 (0.674)
Caucasian	-0.10 (0.921)	0.97 (0.378)	1.40 (0.221)	1.71 (0.147)	0.62 (0.561)
Asian	1.79 (0.133)	0.77 (0.475)	2.31 (0.069)	1.56 (0.179)	0.50 (0.640)
Hepatocellular carcinoma	-0.44 (0.736)	-0.68 (0.618)	-0.03 (0.983)	0.41 (0.753)	0.69 (0.614)
Breast cancer	0.16 (0.900)	0.35 (0.786)	1.02 (0.494)	3.71 (0.168)	0.10 (0.934)
other cancers	2.66 (0.056)	2.74 (0.052)	2.05 (0.110)	2.26 (0.086)	2.05 (0.110)

Table 4. ORs (95% CI) of Sensitivity Analysis

Excluding literature one by one	G vs. A OR (95% CI)	GG vs. AA OR (95% CI)	AG vs. AA OR (95% CI)	GG/AG vs. AA OR (95% CI)	GG vs. AG/AA OR (95% CI)
Over all	1.51 (1.17-1.95)	2.93 (1.50-5.74)	1.47 (1.10-1.97)	1.69 (1.22-2.32)	2.31 (1.23-4.32)
Ferrer-Ferrer (2013)	1.58 (1.22-2.05)	3.28 (1.63-6.60)	1.45 (1.07-1.95)	1.70 (1.21-2.38)	2.67 (1.43-5.00)
Medhi (2013)	1.46 (1.12-1.90)	2.81 (1.38-5.71)	1.43 (1.05-1.94)	1.64 (1.16-2.30)	2.21 (1.14-4.27)
Zagouri (2012)	1.57 (1.20-2.05)	3.34 (1.67-6.69)	1.49 (1.08-2.04)	1.73 (1.22-2.44)	2.63 (1.39-4.98)
Srivastava (2012)	1.44 (1.12-1.85)	2.71 (1.36-5.42)	1.36 (1.04-1.79)	1.56 (1.14-2.12)	2.22 (1.16-4.26)
Wang (2010)	1.59 (1.24-2.05)	3.35 (1.71-6.57)	1.57 (1.17-2.10)	1.82 (1.33-2.48)	2.56 (1.32-4.96)
Rehman (2009)	1.51 (1.15-1.99)	2.74 (1.38-5.46)	1.38 (1.04-1.84)	1.60 (1.15-2.21)	2.25 (1.18-4.29)
Jeng (2008)	1.39 (1.12-1.73)	2.54 (1.33-4.85)	1.43 (1.08-2.06)	1.55 (1.14-2.11)	2.06 (1.11-3.85)
Toth (2007)	1.54 (1.17-2.03)	3.19 (1.52-6.69)	1.49 (1.08-2.06)	1.72 (1.21-2.46)	2.48 (1.25-4.93)
Jalbout (2003)	1.52 (1.15-2.01)	3.06 (1.43-6.55)	1.51 (1.09-2.09)	1.72 (1.20-2.45)	2.37 (1.16-4.83)
Mestiri (2001)	1.51 (1.14-2.00)	2.81 (1.37-5.77)	1.58 (1.19-2.09)	1.78 (1.27-2.50)	2.08 (1.10-3.94)
Chouchane (1997)†	1.48 (1.13-1.92)	2.54 (1.30-4.95)	1.46 (1.08-1.98)	1.65 (1.19-2.30)	2.02 (1.08-3.82)
Chouchane (1997)*	1.48 (1.14-1.93)	2.57 (1.31-5.03)	1.47 (1.08-1.99)	1.66 (1.19-2.32)	2.04 (1.09-3.82)
Li (2010)	1.51 (1.14-1.98)	2.93 (1.41-6.07)	1.50 (1.09-2.06)	1.70 (1.20-2.42)	2.28 (1.16-4.93)
Shibata (2009)	1.58 (1.22-2.05)	3.44 (1.75-6.74)	1.56 (1.15-2.11)	1.80 (1.30-2.50)	2.63 (1.39-4.98)

*† study for the non-Hodgkin's lymphoma. *study for the breast cancer

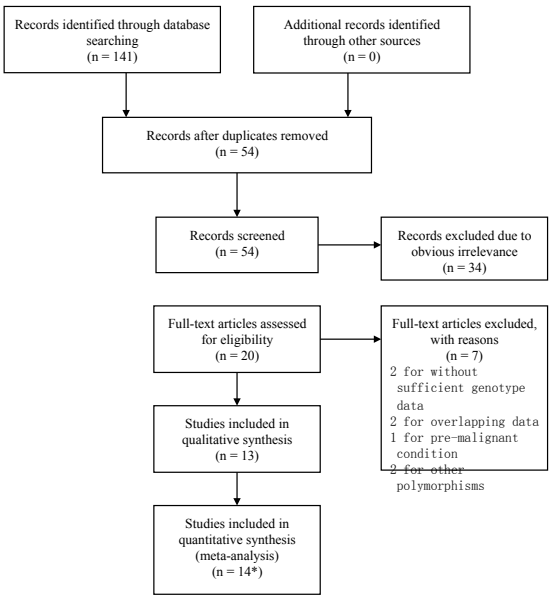

Figure 1. Flow diagram of the study selection process. *one publication included two types of cancers, we extracted data separately for each cancer, thus 14 studies were included

mentioned. According to the cancer types, 3 studies focus on hepatocellular carcinoma, 3 studies on breast cancer, 2 studies on gastric cancer and 6 studies on other cancers (lung cancer, pancreatic cancer, skin cancer, colorectal cancer, nasopharyngeal cancer and non-Hodgkin's lymphoma), respectively. The genotype distributions in the controls of 8 studies were consistent with HWE. The genotyping method in all studies was polymerase chain reaction-restriction fragment length polymorphism.

Meta-analysis

Overall, when all applicable studies were pooled into the meta-analysis, we found that the *HSPA1B* ±1267A/G polymorphism was significantly associated with increased cancer risk in all genetic models (G *vs* A: OR=1.51, 95%CI 1.17-1.95, *p*=0.001; GG *vs* AA: OR=2.93, 95%CI 1.50-5.74, *p*=0.002; AG *vs* AA: OR=1.48, 95%CI 1.10-1.98, *p*=0.009; GG/AG *vs* AA: OR=1.69, 95%CI 1.22-2.33, *p*=0.001; GG *vs* AG/AA: OR=2.31, 95%CI 1.24-4.32, *p*=0.009). In the subgroup analysis stratified by ethnicity, a significantly increased cancer risk was found in Caucasian population (G *vs* A: OR=1.35, 95%CI 1.08-1.69, *p*=0.008; GG/AG *vs* AA: OR=1.36, 95%CI 1.09-1.70, *p*=0.007), but not in Asian population. When stratified by cancer type, the G allele was associated with an increased risk of hepatocellular carcinoma in all genetic models (G *vs* A: OR=2.40, 95% CI 1.47-3.91, *p*<0.001; GG *vs* AA: OR=6.07, 95% CI 2.80-13.19, *p*<0.001; AG *vs* AA: OR=1.80, 95% CI 1.34-2.42, *p*<0.001; GG/AG *vs* AA: OR=2.41, 95% CI 1.51-3.87, *p*<0.001; GG *vs* AG/AA: OR=4.98, 95% CI 3.18-7.79, *p*<0.001), while it seemed to be protective against gastric cancer (GG *vs* AG/AA: OR=0.39, 95%CI 0.20-0.70, *p*=0.007) (Table 2).

Heterogeneity analysis

There was significant heterogeneity among included studies in all comparison models (P_Q<0.001 for all). Thus, we conducted subgroup analyses to explore the sources of heterogeneity. Although the results of subgroup analyses showed the heterogeneity was still significant in Asian populations and other cancer types, the heterogeneity

decreased obviously in Caucasian populations (AG *vs* AA: P_Q=0.140; GG/AG *vs* AA: P_Q=0.562), gastric cancers (G *vs* A: P_Q=0.671; GG *vs* AA: P_Q=0.466; GG/AG *vs* AA: P_Q=0.245; GG *vs* AA/AG: P_Q=0.793), hepatocellular carcinoma (AG *vs* AA: P_Q=0.377; GG *vs* AA/AG: P_Q=0.191), and breast cancer (GG/AG *vs* AA: P_Q=0.291) (Table 2). We further identify the source of heterogeneity by ethnicity, cancer type and HWE with the meta-regression. The results revealed that cancer type (p=0.015), but not ethnicity and HWE (p>0.05) contribute to the source of heterogeneity.

Sensitivity analysis

In order to test the robustness of the results of the meta-analysis, we conducted the sensitivity analysis by sequentially omitting each individual study for all genetic models. The results indicated that the corresponding pooled ORs were not materially altered, which confirmed the stability and reliability of our overall results (Table 4). Furthermore, we performed sensitivity analysis by excluding the studies not conforming to HWE. The results also showed the corresponding pooled ORs were not materially altered in overall comparisons (Table 2).

Publication bias

We carried out Funnel plot and Egger's linear regression test to assess the potential publication bias of the literatures. There was no evidence of funnel plot asymmetry observed in any genetic model of overall studies and subgroup studies (not shown). And the results of Egger's linear regression test also showed no publication bias. Due to small sample size, the Egger's linear regression test was not available for gastric cancer (Table 3).

Discussion

HSP70 is a key chaperone protein that regulates cellular homeostasis in tumor microenvironment and is over expressed on the surface of tumor cells, which induces antitumor immunorecognition by cytotoxic T lymphocytes (Radons and Multhoff, 2005). It has the ability to influence tumor cells proliferation and survival, participate in tumor immunogenicity, and confer resistance to chemotherapy (Ciocca and Calderwood, 2005). Human HSP70 gene is located in the class III region of MHC on chromosome 6p21.3, which contains three main genes (*HSPA1A, HSPA1B* and *HSPA1L*). The most common polymorphisms is at position ±1267 of coding region of *HSPA1B* gene. Several investigators have studied the possible association between ±1267A/G polymorphism and cancer risk. However, the results were inconclusive or even contradictory. In order to obtain a more precise estimation of this association, we performed a meta-analysis including 14 case-control studies with 1, 834 cases and 2, 028 controls to systematically clarify the association between the *HSPA1B* ±1267A/G polymorphism and cancer risk. In overall meta-analysis, the G allele of ±1267A/G polymorphism was found to be significantly associated with an increased cancer risk in all five genetic models. The G allele of ±1267A/G polymorphism may interfere with the secondary structure and stability of mRNA, leading to affect the expression of HSP70, and thus contributes to the predisposition and development of cancers.

We also performed the subgroup analysis to disclose the effects of confounding factors. As for the subgroup analysis by ethnicity, significantly increased cancer risks with G allele of ±1267A/G polymorphism were found in Caucasian populations under allelic comparison and dominant model. However, there was no association between ±1267A/G polymorphism and cancer risk in Asian populations. One potential explanation is that different ethnicities have various genetic backgrounds, which may lead to different degrees of cancer susceptibility (Constantinescu et al., 1975). For example, several GWAS studies have reported polymorphisms at 6p21.3 were associated with lung cancer risk, but they did not exist in Asians according to the HapMap project (Hung et al., 2008; Wang et al., 2008; Broderick et al., 2009). The other reason may be that different ethnicities which live in different regions have various dietary habits and life-styles and expose to multiple environmental factors, and thus yield diverse gene-environment interactions (Latvala et al., 2011; Wu et al., 2012).

In the subgroup analysis stratified by cancer type, the ±1267A/G polymorphism demonstrated varied effect on predisposition to different types of cancer. We detected a significant association between the G allele and an increased risk of hepatocellular carcinoma. However, an opposite association was found in gastric cancer for the GG genotype compared with AG/AA genotypes. This can potentially be explained by the following reasons. First, different types of cancer may have their own genetic etiology. This polymorphism of our interest may have different roles in different cancers. Moreover, there were only 2 or 3 studies relevant for gastric cancer, hepatocellular carcinoma and breast cancer, respectively.

Finally, the huge heterogeneity in this meta-analysis should not be ignored. We observed significant between-study heterogeneity in the pooled analyses in all five genetic models. We further conducted subgroup analyses to explore the sources of heterogeneity. Subgroup analyses stratified by ethnicity and cancer type showed that the heterogeneity decreased substantially in Caucasian population, and for gastric cancer, hepatocellular carcinoma, and breast cancer in some comparison models, but remained significant in Asian population as well as for other cancer types. Subsequently, we investigated the source of heterogeneity by using meta-regression, and the results indicated that cancer type, but not ethnicity or HWE, contributed to the majority source of heterogeneity. Other covariates, such as age, sex, body max index, smoking and drinking status, diet habit etc may also induce such heterogeneity. However, we could not evaluate their potential effects due to the unavailability of data in included studies.

Some limitations should also be acknowledged in our study when interpreting results. First, although overall our analysis included a fairly large sample size (1, 834 cases and 2, 028 controls), after stratifying by cancer type, the sample size for each specific type of

cancer became relatively small, and thus may limited the ability to sufficiently explore the associations. However, our analysis synthesized evidences from all available studies, and further studies with larger power are warranted to better characterize these associations. Second, heterogeneity in our meta-analysis was huge, and meta-regression analysis indicated that cancer type can only explain part of this heterogeneity. As a lack of data for other potential confounders, we could not explore their potential effects. Third, this meta-analysis was based on unadjusted estimates, and a more precise estimation taking account of other confounders such as age, sex, body max index, smoking and drinking status, diet habit, family history and environmental exposures could potentially more accurately estimate the associations. Fourth, not all studies included in our meta-analysis were consistent with HWE. Certain considerations, including potential laboratory and/or genotyping errors, population stratification, and selection bias may apply for those 6 studies which were deviated from HWE. Interpretation of our findings should be cautious considering all these limitations.

In conclusion, our meta-analysis supports that the *HSPA1B* gene ±1267A/G polymorphism may contribute to susceptibility of cancer, though in a Caucasian-specific manner. The G allele probably increases risk of hepatocellular carcinoma while may be protective from gastric cancer. Further well-designed studies with larger sample sizes are warranted to validate these findings and better clarify these associations.

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