RESEARCH COMMUNICATION

Association Between the FAS/FASL Polymorphisms and Gastric Cancer Risk: A Meta-Analysis

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Abstract

Objective: FAS/FASL gene promoter polymorphisms have been repeatedly associated with gastric cancer risk, but findings are inconclusive across studies. To address a more precise estimation of the relationship, a meta-analysis was performed. Methods: Data were collected from the Pubmed, Medline and EMBASE databases, with the last report up to 1 December, 2011. Crude ORs with 95% CIs were used to assess the strength of the association by (1) the additive, (2) the codominant, (3) the dominant, and (4) the recessive models. Results: A total of seven studies, including six studies on FAS -1377G>A polymorphism, five studies on FAS -670A>G polymorphism, and six studies on FASL -844T>C polymorphism, were identified in the current meta-analysis. Overall, an association of FAS -1377G>A (AA versus GG: OR = 1.313, 95% CI = 1.045-1.650, *Ph* = 0.347, I^2 = 10.8) and FASL -844T>C (CC versus TT: OR = 1.352, 95% CI = 1.043-1.752, *Ph* = 0.461, I^2 = 0.0) polymorphisms with gastric cancer was found in the codominant model. However, we did not detect any association between gastric cancer and the FAS -670A>G polymorphism. In the subgroup analysis by ethnicity, similar elevated risks were also observed in Asian population for FAS -1377G>A (AA versus GG: OR = 1.309, 95% CI = 1.041-1.646, *Ph* = 0.240, I^2 = 27.3) and FASL -844T>C (CC versus TT: OR = 1.420, 95% CI = 1.081-1.865, *Ph* = 0.524, I^2 = 0.0) polymorphisms. Conclusions: This meta-analysis indicated that FAS -1377G>A and FASL -844T>C polymorphisms might be associated with gastric cancer risk.

Keywords: Gastric cancer - FAS - FASL - polymorphism - meta-analysis

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Introduction

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer death worldwide. About one million new cases of GC were estimated to have occurred, followed by the lung, breast and colorectal cancer (Ferlay et al., 2010). However, more than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia (mainly in China) (Ferlay et al., 2010). Epidemiological studies have suggested several environmental factors may contributed to the development of GC, including cigarette smoking (Yang et al., 2011; Nomura et al., 2012), alcohol consumption (Yang et al., 2006; Duell et al., 2011), pathogenic infections (Yang et al., 2006; Sivachandran et al., 2012) and nutritional deficiency (Yang, 2000). Nevertheless, only a fraction of exposed individuals actually developed GC during their life, suggesting that genetic makeup may confer susceptibility to GC.

Several common low-penetrant genes have been identified as potential GC susceptibility markers. An important one is FAS (also known as TNFSF6, CD95, or APO-1), a cell surface death receptor, which plays an important role in the apoptosis and cancer development (Nagata and Golstein., 1994). By interaction with its natural ligand FASL (also known as CD95L), a member of the tumor necrosis factor superfamily, FAS triggers the death signal cascade contributing to apoptotic cell death (Itoh et al., 1991; Oehm et al., 1992). Aberrant expression of FAS and/or FASL has been detected in many human cancers, including GC (Walboomers et al., 1999; Takahama et al., 2002; Viard-Leveugle et al., 2003).

Over the last two decades, numerous case-control studies have been performed to clarify the relationship between FAS/FASL polymorphisms and GC risk in human (Ikehara et al., 2006; Hsu et al., 2008; Wang et al., 2009; Zhou et al., 2010; Liu et al., 2011; Kupcinskas et al., 2011; Zhang et al., 2011). The most extensively studied polymorphisms are the G to A substitution at position -1377 (-1377G>A, rs2234767) and A to G substitution at position -670 (-670A>G, rs1800682), and the C to T substitution at position -844 (-844C>T, rs763110) in the

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promoter region of FAS/FASL gene. However, the results of these studies remain conflicting rather than conclusive, partially due to the relative small sample size, different racial and ethnic backgrounds, uncorrected multiple hypothesis testing and publication bias (Zou et al., 2011). To derive a more precise evaluation of the relationship between FAS -1377G>A, -670A>G, and FASL -844T>C polymorphisms and GC susceptibility, we performed a meta-analysis.

Materials and Methods

Identification of eligible studies

We conducted a comprehensive search on English-language articles that examined the association of the FAS/FASL gene promoter polymorphisms with GC using Pubmed, Medline and EMBASE database (last report up to 1 December, 2011). Combinations of keywords: ("FAS" or "CD95"), ("FASL" or "CD95L"), ("polymorphism" or "polymorphisms"), "gastric" and ("cancer" or "carcinoma" or "tumor") were entered as Medical Subject Heading (MeSH) components and as text words. References of identified studies and review articles were checked for other potentially relevant publications. Abstracts or unpublished reports were not considered. If the same patient population was included in several publications, only the study with larger sample size was used in this meta-analysis. For studies including subjects of different ethnic groups, each study should be treated independently.

Eligible studies included in the current meta-analysis should meet the following criterions: (1) it was a case-control study; (2) the study was to clarify the association of FAS/FASL polymorphisms with GC; (3) it presented sufficient data to calculate an odds ratio (OR) with 95% confidence interval (CI). We excluded the studies with family members, because their analysis is based on linkage considerations.

Data extraction

Two investigators (Tian J and Pan F) independently extracted the data according to the standard protocol, and the result was reviewed by a third investigator (Ye DQ). Discrepancies were resolved by discussion with our research team. The following information was extracted from each study: the first author's name, publication year, country of origin, racial ancestry, number of genotyped cases and controls, source of control group, genotyping method, control matching method, polymorphisms, studying period and available genotype distributions information.

Meta-analysis methods

Meta-analysis was performed for the polymorphisms that had been investigated in at least three studies. Pooled ORs with 95% CIs were used to assess the strength of association between the FAS/FASL polymorphisms and susceptibility to GC. We evaluated the risk of (1) additive model (minor allele versus major allele); (2) codominant model (heterozygous versus common homozygous carriers and rare homozygous versus common homozygous carriers); (3) dominant model (rare allele carriers versus common homozygous carriers); (4) recessive model (rare homozygous carriers versus common allele carriers). The between-study heterogeneity was assessed using the Chi-square test-based Q-statistic (Cochran, 1954). If a significant Q-statistic ($P < 0.1$) was observed, indicating heterogeneity across studies, the random-effects model was used (DerSimonian and Laird, 1986). Otherwise, the fixed-effect model would be explored (Mantel and Haenszel, 1959). The random-effects model assumes different studies show substantial diversity and assesses both within-study sampling error and between-study variation (DerSimonian and Laird, 1986). The fixed-effect model assumes that all of the studies are estimating the same underlying effect and considers only within-study variance (Mantel and Haenszel, 1959). We also quantified the effect of heterogeneity using $I^2 = 100\% \times (Q\text{-df})/Q$ (Higgins and Thompson, 2002), which ranges between 0 and 100%, and measures the degree of inconsistency in the studies by calculating what proportion of the total variation across studies attributed to heterogeneity rather than chance (Higgins et al., 2003). The overall estimate of risk was obtained by DerSimonian and Laird method in a random-effects model or Mantel-Haenszel method in a fixed-effects model in the presence ($P \leq 0.1$ or $I^2 > 50\%$) or absence ($P > 0.1$ or $I^2 \leq 50\%$) of heterogeneity, respectively (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986). Pooled OR with 95% CI was performed weighting individual OR by the inverse of their variance. The significance of the pooled OR was determined by the Z-test.

A chi-square test was used to estimate the Hardy-Weinberg equilibrium (HWE) among the control individuals to compare the observed genotype frequencies with the expected ones. The power analysis of each study was done using the statistical program G *Power 3.1 at the level 0.05 level of significance, assuming an OR of 1.5 (small effect size) (Faul et al., 2009).

Evaluation of publication bias

We estimated the potential publication bias by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). If there was publication bias, the funnel plot would be asymmetric. Funnel plot asymmetry was further determined by the method of Egger's linear regression test (Egger et al., 1997), which measures funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the t-test, and $P < 0.05$ was considered representative of statistically significant publication bias.

All the statistical analyses were conducted by STATA version 7.0 (Stata Corporation, College Station, TX, USA). A P-value less than or equal to 0.05 was considered statistically significant.

Results

Studies included in the meta-analysis

A total of seven studies, six studies for FAS -1377G>A and FASL -844T>C polymorphisms, respectively, and

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

First author	Year	Country	Ethnicity	Sample size Case	Control	Sources of controls	Genotyping method	Control matching method	Polymorphisms	Studying period	Power#
Ikehara SK	2006	Japan	Asian	271	271	HB	PCR-RFLP	Age, sex	FAS -670	2001 to 2003	64.4
Hsu PI	2008	Taiwan	Asian	86	101	HB	PCR-RFLP	NM (age, sex)	FAS -670, FAS -1377, FASL -844	NA	27.7
Wang M	2009	China	Asian	332	324	PB	PCR-RFLP	Age, sex	FAS -670, FAS -1377, FASL -844	2003 to 2005	72.6
Zhou RM	2010	China	Asian	262	524	HB	PCR-RFLP	Age, sex, ethnic	FAS -670, FAS -1377, FASL -844	2003 to 2006	80.1
Zhang W	2011	China	Asian	375	496	HB	PCR-RFLP	Age, sex, ethnic	FAS -1377, FASL -844	1999 to 2009	83.9
Kupcinskas J	2011	*Three	Caucasian	114	238	HB	Taqman	NM (age, sex)	FAS -670, FAS -1377, FASL -844	1998 to 2008	46.7
Liu L	2011	China	Asian	344	324	HB	PCR-RFLP	Age, sex, ethnic	FAS -1377, FASL -844	1997 to 2003	73.4

*Germany, Lithuania, Latvia; #$\alpha = 0.05$, OR = 1.5; HB, hospital-based case-control study; PB, population-based case-control study; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; NA, not available; NM, not matched

Table 2. Distributions of FAS Gene Genotypes and Alleles Among Patients and Controls

First author	Year	Case			Control			Case		Control		P^{HWE}
FAS -1377		GG	GA	AA	GG	GA	AA	G	A	G	A	
Hsu PI	2008	27	42	17	33	49	19	96	76	115	87	0.914
Wang M	2009	137	155	40	148	141	35	429	235	437	211	0.87
Zhou RM	2010	124	117	21	225	251	48	365	159	701	347	0.062
Zhang W	2011	138	171	66	197	246	53	447	303	640	352	0.064
Kupcinskas J	2011	95	18	1	197	40	1	208	20	434	42	0.492
Liu L	2011	130	155	59	127	157	40	415	273	411	237	0.424
FAS -670		AA	AG	GG	AA	AG	GG	A	G	A	G	
Ikehara SK	2006	62	141	68	71	130	70	265	277	272	270	0.504
Hsu PI	2008	25	47	14	33	48	20	97	75	114	88	0.736
Wang M	2009	116	172	44	132	148	44	404	260	412	236	0.806
Zhou RM	2010	105	121	36	186	266	72	331	193	638	410	0.133
Kupcinskas J	2011	31	62	21	70	127	41	124	104	267	209	0.199
FASL -844		TT	TC	CC	TT	TC	CC	T	C	T	C	
Hsu PI	2008	7	32	47	14	44	43	46	126	72	130	0.612
Wang M	2009	23	122	187	28	127	169	168	496	183	465	0.554
Zhou RM	2010	13	101	148	24	174	326	127	397	222	826	0.899
Zhang W	2011	32	120	223	48	237	211	184	566	333	659	0.112
Kupcinskas J	2011	55	52	7	124	94	20	162	66	342	134	0.715
Liu L	2011	30	115	199	31	160	133	175	513	222	426	0.083

HWE, Hardy-Weinberg equilibrium

Table 4. Tests for Publication Bias (Egger's Test) in Overall Population

Polymorphism	Comparison	Egger's test
FAS -1377	A vs. G	0.591
	AA vs. GG	0.743
	AG vs. GG	0.928
	AG/AA vs. GG	0.859
	AG/GG vs. AA	0.744
FAS -670	G vs. A	0.856
	GG vs. AA	0.978
	AG vs. AA	0.562
	GG/AG vs. AA	0.605
	AA/AG vs. GG	0.489
FASL -844	C vs. T	0.78
	CC vs. TT	0.536
	CT vs. TT	0.537
	CC/CT vs. TT	0.402
	CT/TT vs. CC	0.652

five studies for FAS -670A>G polymorphism, met the inclusion criteria (Ikehara et al., 2006; Hsu et al., 2008; Wang et al., 2009; Zhou et al., 2010; Kupcinskas et al., 2011; Liu et al., 2011; Zhang et al., 2011). The characteristics of each article are listed in Table 1. Seven separate studies consisted of six Asian and one Caucasian. Of these articles, six studies were hospital-based, and one study was population-based. We calculated the expected power of each study to demonstrate an association between FAS/FASL polymorphisms and GC (Table 1). The results of HWE test for the genotypes distributions in control population are shown in Table 2. All the eligible studies were consistent in HWE.

Meta-analysis

A summary of the meta-analysis for the FAS/FASL promoter polymorphisms and GC risk is given in Table 3.

Evaluation of FAS -1377G>A polymorphism and association with GC

The association between FAS -1377G>A polymorphism and GC was investigated in six separate studies including 1513 cases and 2007 controls. No significant heterogeneity was observed and the original data were combined by means of the fixed-effects models. An association of FAS -1377G>A polymorphism with GC was found in the contrast of AA versus GG (OR = 1.313, 95% CI = 1.045-1.650, *Ph* = 0.347, I^2 = 10.8) when all studies were pooled into the meta-analysis. Owing to the limited literature in Caucasian population and population-based controls, subgroup stratification was only performed in Asian population and hospital-based studies. Similar association was also found in Asians (OR = 1.309, 95% CI = 1.041-1.646, *Ph* = 0.240, I^2 = 27.3) and hospital-based studies (OR = 1.333, 95% CI = 1.033-1.722, *Ph* = 0.237, I^2 = 27.6).

Table 3. Main Results of Pooled ORs in the Meta-Analysis

Polymorphism	Study groups(n)	Comparison	Test of association			Test of heterogeneity			Model
			OR(95%CI)	Z	*P*	χ^2	*P*	I^2	
FAS -1377	Total(6)	A vs. G	1.092(0.985-1.210)	1.68	0.094	5.37	0.372	7	F
		AA vs. GG	1.313(1.045-1.650)	2.34	0.02	5.61	0.347	10.8	F
		AG vs. GG	0.987(0.851-1.144)	0.18	0.857	2.28	0.81	0	F
		AG/AA vs. GG	1.044(0.907-1.201)	0.6	0.551	3.27	0.659	0	F
		AG/GG vs. AA	0.994(0.877-1.126)	0.1	0.922	0.77	0.979	0	F
	Asian(5)	A vs. G	1.095(0.987-1.216)	1.71	0.088	5.26	0.262	23.9	F
		AA vs. GG	1.309(1.041-1.646)	2.3	0.021	5.5	0.24	27.3	F
		AG vs. GG	0.990(0.850-1.153)	0.13	0.897	2.24	0.691	0	F
		AG/AA vs. GG	1.049(0.908-1.212)	0.64	0.519	3.19	0.527	0	F
		AG/GG vs. AA	0.995(0.869-1.138)	0.08	0.938	0.77	0.942	0	F
	HB(5)	A vs. G	1.081(0.964-1.213)	1.33	0.183	5.24	0.263	23.7	F
		AA vs. GG	1.333(1.033-1.722)	2.21	0.027	5.53	0.237	27.6	F
		AG vs. GG	0.940(0.796-1.110)	0.73	0.466	0.71	0.951	0	F
		AG/AA vs. GG	1.007(0.860-1.179)	0.09	0.931	2.31	0.678	0	F
		AG/GG vs. AA	0.972(0.846-1.116)	0.41	0.685	0.25	0.993	0	F
FAS -670	Total(5)	G vs. A	1.025(0.913-1.151)	0.42	0.674	2	0.735	0	F
		GG vs. AA	1.040(0.815-1.327)	0.32	0.752	0.83	0.934	0	F
		AG vs. AA	1.091(0.911-1.307)	0.94	0.345	5.33	0.255	24.9	F
		GG/AG vs. AA	1.075(0.905-1.276)	0.82	0.411	4.52	0.34	11.6	F
		AA/AG vs. GG	1.027(0.829-1.273)	0.25	0.806	0.46	0.978	0	F
	Asian(4)	G vs. A	1.018(0.900-1.153)	0.29	0.775	1.92	0.59	0	F
		GG vs. AA	1.024(0.788-1.329)	0.18	0.861	0.72	0.868	0	F
		AG vs. AA	1.089(0.898-1.321)	0.87	0.384	5.38	0.149	43.7	F
		GG/AG vs. AA	1.069(0.890-1.284)	0.72	0.474	4.5	0.213	33.3	F
		AA/AG vs. GG	1.045(0.830-1.316)	0.37	0.709	0.3	0.96	0	F
	HB(4)	G vs. A	0.991(0.866-1.135)	0.13	0.9	1.12	0.772	0	F
		GG vs. AA	1.009(0.761-1.337)	0.06	0.949	0.66	0.883	0	F
		AG vs. AA	1.006(0.811-1.248)	0.06	0.955	3.49	0.322	14.1	F
		GG/AG vs. AA	0.999(0.814-1.225)	0.01	0.99	2.84	0.417	0	F
		AA/AG vs. GG	1.027(0.805-1.311)	0.21	0.831	0.46	0.928	0	F
FASL -844	Total(6)	C vs. T	1.238(0.997-1.536)	1.94	0.053	18.76	0.002	73.4	R
		CC vs. TT	1.352(1.043-1.752)	2.27	0.023	4.64	0.461	0	F
		CT vs. TT	0.996(0.784-1.264)	0.04	0.97	3.95	0.556	0	F
		CC/CT vs. TT	1.168(0.931-1.465)	1.34	0.181	1.4	0.924	0	F
		CT/TT vs. CC	0.986(0.788-1.234)	0.12	0.905	2.35	0.799	0	F
	Asian(5)	C vs. T	1.276(0.999-1.630)	1.95	0.051	17.54	0.002	77.2	R
		CC vs. TT	1.420(1.081-1.865)	2.52	0.012	3.21	0.524	0	F
		CT vs. TT	0.918(0.696-1.212)	0.6	0.547	2.7	0.61	0	F
		CC/CT vs. TT	1.168(0.897-1.520)	1.15	0.248	1.4	0.843	0	F
		CT/TT vs. CC	0.933(0.710-1.226)	0.5	0.616	1.84	0.764	0	F
	HB(5)	C vs. T	1.255(0.960-1.641)	1.66	0.097	18.3	0.001	78.1	R
		CC vs. TT	1.353(1.013-1.807)	2.05	0.041	4.64	0.326	13.8	F
		CT vs. TT	0.966(0.745-1.253)	0.26	0.796	3.62	0.46	0	F
		CC/CT vs. TT	1.150(0.898-1.472)	1.11	0.269	1.3	0.861	0	F
		CT/TT vs. CC	0.963(0.756-1.227)	0.3	0.761	2.08	0.721	0	F

HB, hospital-based case-control study; OR, odds ratio; CI, confidence interval; R, random-effects model; F, fixed-effects model

Evaluation of FAS -670A>G polymorphism and association with GC

There were five studies with 1065 cases and 1458 controls examining the association of FAS -670A>G polymorphism with GC. The Q test of heterogeneity was not significant and we conducted analyses using the fixed-effects models. We did not detect any association between FAS -670A>G and GC in the overall group (G vs. A: OR = 1.025, 95% CI = 0.913-1.151, $Ph = 0.735$, $I^2 = 0.0$; GG vs. AA: OR = 1.040, 95% CI = 0.815-1.327, Ph = 0.934, $I^2 = 0.0$; AG vs. AA: OR = 1.091, 95% CI = 0.911-1.307, $Ph = 0.255$, $I^2 = 24.9$;Dominant model: OR = 1.075, 95% CI = 0.905-1.276, $Ph = 0.340$, $I^2 = 11.6$; Recessive model: OR = 1.027, 95% CI = 0.829-1.273, $Ph = 0.978$, $I^2 = 0.0$). Similar results were observed in the subgroup analyses by race and sources of controls, more details were presented in Table 3.

Evaluation of FASL -844T>C polymorphism and association with GC

We found six separate studies (1513 cases and 2007 controls) investigating the association between FASL -844T>C polymorphism and GC risk. The Q test of heterogeneity was not significant and we conducted analyses using the fixed-effects models, except in the comparison of C versus T. An association was found in the overall population when examining the contrast of CC versus TT (OR = 1.352, 95% CI = 1.043-1.752, $Ph = 0.461$, $I^2 = 0.0$). Meanwhile, we performed group-specific meta-analysis in Asian population and hospital-based

studies. Similarly, elevated risks were observed among Asians (OR = 1.420, 95% CI = 1.081-1.865, *Ph* = 0.524, I^2 = 0.0) and groups with hospital-based controls for CC versus TT (OR = 1.353, 95% CI = 1.013-1.807, *Ph* = 0.326, I^2 = 13.8).

Publication bias

The shapes of the funnel plots revealed no obvious asymmetry (figures not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. Also, the results still did not suggest any evidence of publication bias (Table 4).

Discussion

Apoptosis is one of the most important regulatory mechanisms to all multicellular organisms for normal development and tissue homeostasis (Reed, 2000). Inappropriate regulation of apoptosis contributes to a number of human disorders, including GC (Thompson, 1995; Hajra and Liu, 2004). There were two main apoptotic pathways in mammalian cells: the extrinsic or receptor-mediated pathway and the intrinsic or mitochondrial pathway (Nicholson and Thornberry, 1997; Ashkenazi and Dixit, 1999; Budihardjo et al., 1999). FAS is a cell surface receptor that belongs to the tumor necrosis factor receptor family. By interaction with its natural ligand FASL, FAS initiates the extrinsic apoptotic pathway (Itoh et al., 1991; Oehm et al., 1992; Suda et al., 1993). Accumulating evidence showed that aberrant expression of FAS and FASL in many human cancers, including GC (Walboomers et al., 1999; Takahama et al., 2002; Viard-Leveugle et al., 2003; Gryko et al., 2011). It has been proposed that down-regulation of FAS may protect tumor cells from elimination by anti-tumor immune responses, whereas up-regulation of FASL may increase the ability of tumor cells to counterattack the immune system by inducing apoptosis of FAS-sensitive lymphocytes (Griffith et al., 1995; Strand et al., 1996; Reichmann, 2002). Therefore, it is reasonable to speculate that FAS/FASL system may play a crucial role in the pathogenesis of GC. In recent years, genetic variants of the FAS/FASL in GC have drawn increasing attention. Growing number of studies have suggested that the -1377G>A and -670A>G polymorphisms in the promoter region of FAS gene, and the -844T>C polymorphism in the promoter region of FASL were emerging as susceptibility loci for GC. However, the results were inconclusive. To better understand the relationship between FAS/FASL polymorphisms (FAS -1377G>A, -670A>G and FASL -844T>C) and GC risk, a meta-analysis was performed.

Overall, our results indicated that the variant genotypes of the FAS -1377G>A and FASL -844T>C polymorphisms but not the FAS -670A>G polymorphism were associated with susceptibility to GC (FAS -1377G>A: AA vs. GG: OR = 1.313, 95% CI = 1.045-1.650, *Ph* = 0.347, I^2 = 10.8; FASL -844T>C: CC vs. TT: OR = 1.352, 95% CI = 1.043-1.752, *Ph* = 0.461, I^2 = 0.0). This finding is biologically plausible. It has been proven that as compared with the -1377G allele, the -1377A allele had a greatly reduced ability to bind transcription factor stimulatory protein 1, whereas the -670A and G alleles had similar ability to bind transcription factor signal transducers and activators of transcription 1 (Sibley et al., 2003). As an important transcriptional activator, if the binding ability of stimulatory protein 1 to the FAS -1377A allele is reduced, decreased expression of FAS in cells carrying the FAS -1377AA genotype was expected (Huang et al., 1997; Sibley et al., 2003). It has been shown that the FASL -844T>C polymorphism has a substantial impact on promoter activity of the FASL gene in an in vitro assay system because of its location in a binding motif for transcription factor CAAT/ enhancer-binding protein β (Wu et al., 2003). Moreover, this variation strongly affected the FASL expression on ex vivo-stimulated T cells (Sun et al., 2005). Activation-induced cell death (AICD) of T lymphocytes may help malignant cells to escape from killing by natural killing cells (Chappell and Restifo, 1998; Green et al., 2003). It has been proposed that the FASL -844C allele had a higher expression on T cells and was associated with an enhanced rate of AICD of T cells, which may result in less powerful immune surveillance and increase the susceptibility to cancer compared with the -844T allele (Sun et al., 2005).

Conspicuous geographic variation exists in the incidence of GC between regions. The highest incidence is in northeast Asia, intermediate incidences occur in Europe and South America, and North America, Africa, south Asia and Oceania are low incidence regions (Hartgrink et al., 2009). Population differences may enlighten some genetic risk factors that are specific towards certain ethnic groups, which may help elucidate the ethnic differences in terms of prevalence and severity. To explore whether the FAS/FASL polymorphisms are associated with GC risk in different genetic backgrounds, subgroup analysis based on ethnicity was performed. We found an association of FAS -1377 G>A and FASL -844T>C polymorphisms with GC among Asians (FAS -1377G>A: AA vs. GG: OR = 1.309, 95% CI = 1.041-1.646, *Ph* = 0.240, I^2 = 27.3; FASL -844T>C: CC vs. TT: OR = 1.420, 95% CI = 1.081-1.865, *Ph* = 0.524, I^2 = 0.0). Similar association was not replicated in Caucasian population, suggesting a possible role of ethnic differences and the environment they lived in (Hirschhorn et al., 2002). Other factors such as selection bias and different matching criteria may also play a role. Considering only one study carried out in Caucasian population, the result might be not reliable.

Some limitations in this meta-analysis should be acknowledged. Firstly, most of eligible studies involved in the current meta-analysis were hospital-based case-control studies, which inevitably suffer selection bias (Knottnerus., 1987). However, each study was in HWE, suggesting the controls could well represent the general population. Secondly, there might be a potential English language bias in the current study, because this meta-analysis only contained the English literature. It was possible that there were differences between English language literature and other language literature. Thirdly, in the subgroup analysis based on ethnicity, only one study containing 271 cases and 271 controls was performed in Caucasian population, there may not be enough statistical power to obtain the real relationship. Thus, our result of subgroup meta-analysis should be interpreted with caution, and further

studies with larger sample size are still needed, especially in Caucasians. Fourthly, this meta-analysis was based on unadjusted estimates, while a more precise analysis could be performed if individual data was available, which would allow for an adjustment estimate by other co-variants, including age, sex, and environmental factors. Finally, meta-analysis remains a retrospective research, which is subject to the methodological deficiencies of the included studies. To minimize the likelihood of bias, we developed a detailed protocol before initiating the study, performed a meticulous search for eligible studies and used explicit methods for data extraction and statistical analysis.

In summary, our meta-analysis suggests that there may be an association of FAS -1377 G>A and FASL -844 T>C polymorphisms with GC. To reach a definitive conclusion, further gene-gene and gene-environment interaction studies based on larger sample size are still needed.

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