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Quantitative assessment of the relationship between Fas/FasL genes polymorphisms and head and neck cancer risk

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Abstract

Background: Molecular epidemiological studies have demonstrated a closer association between Fas/FasL polymorphisms and head and neck cancer (HNC) risk, and the results of these published studies were inconsistent. We therefore performed this meta-analysis to explore the associations between Fas/FasL polymorphisms and HNC risk.

Methods: Four online databases (PubMed, Embase, CNKI, and Wanfang) were searched. Odds ratios (ORs) with 95% confidence interval (95% CIs) were calculated to assess the association between Fas -670A>G, Fas -1377G>A, and FasL -844C>T polymorphisms and HNC risk. In addition, heterogeneity, accumulative/sensitivity analysis, and publication bias were conducted to check the statistical power.

Results: Overall, 9 related publications (20 independent case–control studies) involving 3179 patients and 4217 controls were identified. Significant association of protective effects was observed between FasL -844C>T polymorphism and HNC risk in codominant and dominant model models (CT vs CC: OR = 0.89, 95% CI = 0.79–1.00, P = .05, I^2 = 38.3%, CT+TT vs CC: OR = 0.88, 95% CI = 0.79–0.98, P = .02, I^2 = 35.8%). Furthermore, the similar protective effects were observed the subgroup analysis of in Asian population and population-based controls group.

Conclusion: Our meta-analysis indicated that FasL -844C>T polymorphism plays a protective role against HNC development, but the Fas -670A>G and Fas -1377G>A polymorphisms maybe not associated with HNC risk.

Abbreviations: 95%CIs = 95% confidence intervals, FasL = Fas ligand, HNC = head and neck cancer, HPV = human papillomavirus, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, ORs = odds ratios.

Keywords: Fas, FasL, head and neck cancer, polymorphism

1. Introduction

Head and neck cancer (HNC) is one of the most common types of carcinoma, which is derived from the malignant epithelial cells of the oral cavity, nasal cavity, and the upper respiratory and digestive systems.[1,2] In 2017, there were estimated to be more than 63,030 new HNC cases, which resulted in approximately 13,360 mortalities in the United States and accounted for more than 3.73% of new affected cancers and 2.22% of cancer-related mortalities.[3] HNC was considered as the eighth most common type of cancer worldwide in 2009.[4] The 5-year survival rate has been increasing in recent decade years; however, the pathogenesis of HNC remains unclear.[5,6] Alcohol and tobacco use are the most important effectors that contributed to cancer development.[7,8] Other external factors, including chronic inflammation, human papillomavirus (HPV) infection, vitamin deficiencies, and mental depression, have been suggested to be associated with HNC occurrence.[9–13] In recent decades, the etiology of HNC has attracted increasing attention; however, the variation in cancer susceptibility between different populations has not yet been fully elucidated.

Over the past decade, a large number of studies have suggested that apoptosis plays a vital role in the development of cancer.[14,15] The Fas/Fas ligand (FasL) mediated signaling pathway is one of the most important apoptosis signaling pathways, and the interaction of Fas with FasL regulates numerous physiological and pathological processes that are mediated through programmed cell death.[16] Fas, as known as cluster of differentiation 95 (CD95), tumor necrosis factor

superfamily 6 (TNFSF6), and apoptosis antigen 1(APO-1), is a type I cell surface glycoprotein that can transmit apoptotic signals by binding to its natural ligands FasL.[17] It is a member of the tumor necrosis factor (TNF) receptor superfamily, and has a molecular mass greater than 43 kDa.[18] FasL is an extensively glycosylated molecule and a type II membrane protein with a molecular mass greater than 36 kDa, which can trigger cell apoptosis via cross-linking of the death-inducing receptor, Fas.[19] Certain previous studies have reported that the abnormal expression of Fas and FasL may be conducive to tumor development and progression.[20,21] In addition, specific functional variants of the *Fas* and *FasL* genes may impair the corresponding apoptotic signal transduction, which contributes to high susceptibility to cancer.[22,23] To our knowledge, Fas -670A>G (rs1800682), -1377G>A (rs2234767), and FasL -844C>T (rs763110) are the most common single nucleotide polymorphisms (SNPs) loci, which have been suggested to regulate the Fas/FasL system transcription and expression levels. In 2006, Jrad et al[24] published the first study investigating the association between the Fas -670A>G polymorphism and HNC risk (nasopharyngeal cancer), and demonstrated a significantly increased risk of HNC in carriers of the G allele heterozygote and homozygote variants in a Tunisian population. Subsequently, numerous epidemiological studies have been performed to investigate the association between the 3 FAS/FASL promoter polymorphisms and the risk of HNC; however, the results were not consistent. Therefore, we performed this comprehensive meta-analysis involving all related publications to assess a more precise association between the Fas -670A>G, -1377G>A, and FasL -844C>T polymorphisms and HNC risk.

2. Materials and methods

This meta-analysis was designed and performed according to the guideline of the preferred reporting items for systematic reviews and meta-analyses (PRISMA Compliant) statement.[25] All included data were based on published studies, and no ethical issues were involved.

2.1. Literature search

A total of 4 online electronic databases (PubMed, Embase, CNKI, and Wanfang) were searched for the following terms: "Fas," "Fas ligand," "FasL," "head and neck cancer," "polymorphism," and "variant," up to September 1, 2017. The combined phrases were also used to examine all genetic studies investigating on the association between HNC and Fas/FasL polymorphisms. Only articles written in English and Chinese were selected. The following search strategy was used:

#1 Fas
#2 Fas ligand
#3 FasL
#4 rs1800682
#5 rs2234767
#6 rs763110
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 polymorphism
#9 variant
#10 mutation
#11 #8 OR #9 OR #10
#12 head and neck cancer
#13 oral cancer
#14 nasopharyngeal cancer
15 larynx cancer
16 pharynx cancer
#17 #12 OR #13 OR #14 OR #15 OR #16
#18 #7 AND #11 AND #17

2.2. Eligibility criteria

All included studies were selected according to the following inclusion criteria: case-control studies focusing on the association between Fas/FasL polymorphisms and HNC risk; studies providing sufficient information on genotype distribution and frequency data to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs); studies published in English and Chinese; and the largest sample set or most recent samples were included when duplicate reports were present with the same subjects and objectives.

2.3. Data extraction

Two authors (Zhang and Jiang) independently extracted the following information from all included studies: name of the first author, publishing date, country, or region where the study was performed, patient ethnicity (Asian/Caucasian), design of the controls, sample sizes for patients and healthy controls, genotype distribution frequency data, genotyping method, Hardy–Weinberg equilibrium (HWE) for the controls, minor allele frequency (MAF) in control group, and cancer type.

2.4. Statistical analysis

Crude ORs with 95% CIs were evaluated in order to examine the strength of association between the Fas -670A>G, -1377G>A, and FasL -844C>T polymorphisms and HNC risk. For example, the following 5 genetic models of the Fas -670A>G locus were calculated: allele contrast (G vs A), codominant models (AG vs AA and GG vs AA), dominant model (AG+GG vs AA), and recessive model (GG vs AA+AG). Similar genetic models were also used to assess the other 2 loci (Fas -1377G>A and FasL -844C>T). Stratified assessments were also performed according to HWE status, ethnicity difference, and control design. Heterogeneity was evaluated by Cochran Q test and I^2 statistics.[26] The fixed-effect model (the Mantel–Haenszel method) was used when the I^2 value was less than 40%.[27] In other cases, a random-effects model (DerSimonian and Laird method) was used.[28,29] Meta-regression was conducted to investigate analyses that exhibited heterogeneity. In addition, meta-regression was conducted in some genetic models with subgroup variables (HWE status, ethnicity diversity, control design, and cancer type) to analyze what is the responsible reason for the emergence of heterogeneity. Cumulative meta-analyses were performed to examine the changes in results when additional studies were added. Furthermore, sensitivity analyses were conducted to investigate the stability of the results when studies were removed one by one. Both Egger linear regression and Begg funnel plots were used to investigate the potential publication bias.[30,31] All statistical evaluations were performed using STATA version 14.0 (Stata Corporation, College Station, TX). $P < .05$ was considered to indicate a statistically significant difference.

3. Result

3.1. Study characteristics

First, a total of 261 published relevant articles were accessed by systematic literature searches. The study selection process is shown in Fig. 1. In accordance with the eligibility criteria, 78 studies were excluded in the first step of duplicate screening, 164 studies were

Figure 1. Flow diagram of the study selection process.
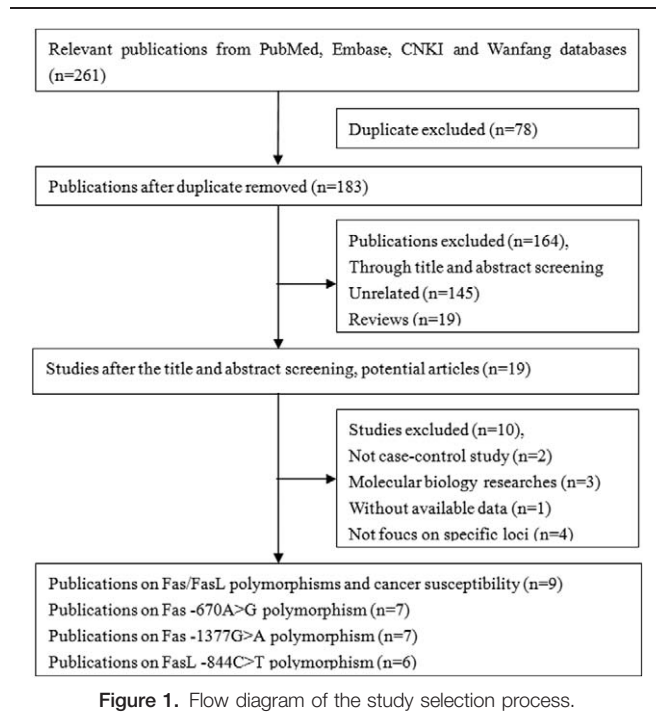
subsequently removed for title and abstract review, and 10 studies were removed because they were not case–control studies, molecular biology research, or without available data and not focused on specific loci. Eventually, 9 publications (20 independent case–control studies) involving 3179 patients and 4217 controls were selected,[24,32–39] including 7 case–control studies investigating Fas -670A>G,[24,32,34,35,37–39] 7 case–control studies investigating Fas -1377G>A,[32,33,35–39] and 6 case–control studies investigating FasL -844C>T,[32,35–39] respectively. Furthermore, 6 publications involved Asian populations,[34–39] and 3 studies involved Caucasian populations.[24,32,33] Regarding the HWE in controls, 1 case–control study deviated the HWE for the Fas -670A>G polymorphism[35] and Fas -1377G>A polymorphism,[37] and 2 case–control studies for the FasL -844C>T polymorphism.[36,39] The detailed characteristics of the included studies are summarized in Table 1.

3.2. Quantitative analysis

3.2.1. Fas -670A>G polymorphism and HNC risk. A total of 7 included case–control studies with 2341 cases and 2960 controls focused on the association between the Fas -670A>G polymorphism and HNC risk. Overall, the combined results did not reveal any significant impact of this SNP locus on HNC in 4 genetic models (G vs A: OR = 1.12, 95% CI = 0.98–1.28, P = .11, I^2 = 61.8%; GG vs AA: OR = 1.26, 95% CI = 0.94–1.69, P = .13, I^2 = 64.3%; AG+GG vs AA: OR = 1.18, 95% CI = 0.97–1.43, P = .09, I^2 = 55.0%; GG vs AA+AG: OR = 1.14, 95% CI = 0.92–1.41, P = .25, I^2 = 50.5%) (Table 2, Fig. 2A for AG+GG vs AA model),

Table 1

Characteristics of included studies on Fas/FasL polymorphisms and head and neck cancer risk.

							Genotype distribution								
							Case			Control					
							Fas -670A>G								
First author	Year	Country/Region	Racial	Source of controls	Case	Control	AA	AG	GG	AA	AG	GG	Genotyping methods	P for HWE*	MAF in control	Type
Bel Hadj Jrad et al[24]	2006	Tunisia	Caucasian	PB	170	224	28	91	51	70	114	40	PCR-RFLP	.59	0.43	NPC
Zhang et al[32]	2006	USA	Caucasian	PB	721	1234	191	363	167	377	599	258	PCR-RFLP	.48	0.45	HNC
Zhu et al[34]	2010	China	Asian	PB	237	264	79	124	34	93	132	39	PCR-RFLP	.48	0.40	NPC
Wang et al[35]	2010	China	Asian	PB	294	333	90	144	60	106	180	47	PCR-RFLP	.03	0.41	OC
Karimi et al[37]	2013	Indian	Asian	HB	139	126	32	88	19	41	67	18	PCR-RFLP	.26	0.41	OC
Wang et al[38]	2013	China	Asian	PB	300	300	124	140	37	122	136	41	PCR-RFLP	.75	0.36	LLC
Daripally et al[39]	2015	India	Asian	HB	535	525	149	226	104	140	224	116	PCR-RFLP	.16	0.48	OC
							Fas -1377G>A								
							GG	GA	AA	GG	GA	AA				
Zhang et al[32]	2006	USA	Caucasian	PB	721	1234	562	142	17	957	264	13	PCR-RFLP	.27	0.12	HNC
Ho et al[33]	2008	USA	Caucasian	PB	154	510	126	24	4	400	100	10	PCR-RFLP	.21	0.12	SC
Wang et al[35]	2010	China	Asian	PB	294	333	95	141	58	115	165	53	PCR-RFLP	.63	0.41	OC
Cao et al[36]	2010	China	Asian	PB	582	613	141	264	171	172	303	133	PCR-RFLP	.98	0.47	NPC
Karimi et al[37]	2013	Indian	Asian	HB	139	126	88	42	9	84	30	12	PCR-RFLP	.01	0.21	OC
Wang et al[38]	2013	China	Asian	PB	300	300	142	133	25	138	124	38	PCR-RFLP	.23	0.33	LLC
Daripally et al[39]	2015	India	Asian	HB	535	525	232	206	44	236	201	34	PCR-RFLP	.32	0.29	OC
							FasL -844C>T								
							CC	CT	TT	CC	CT	TT				
Zhang et al[32]	2006	USA	Caucasian	PB	721	1234	323	316	82	522	551	161	PCR-RFLP	.41	0.35	HNC
Wang et al[35]	2010	China	Asian	PB	294	333	151	126	17	182	123	28	PCR-RFLP	.27	0.27	OC
Cao et al[36]	2010	China	Asian	PB	582	613	297	217	49	295	276	39	PCR-RFLP	.02	0.29	NPC
Karimi et al[37]	2013	Indian	Asian	HB	139	126	22	51	66	22	57	47	PCR-RFLP	.51	0.60	OC
Wang et al[38]	2013	China	Asian	PB	300	300	181	104	15	146	126	28	PCR-RFLP	.91	0.30	LLC
Daripally et al[39]	2015	India	Asian	HB	535	525	156	228	123	135	208	137	PCR-RFLP	<.01	0.50	OC

*HWE in control.

HB = hospital-based, HNC = head and Neck cancer, LLC = larynx and hypopharynx cancer, MAF = minor allele frequency in control group, NPC = nasopharyngeal cancer, OC = oral cancer, PB = population-based PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SC = salivary cancer.

Table 2

Summary ORs and 95% CI of Fas/FasL polymorphisms and head and neck cancer risk.

Fas -670A>G

Locus	N*	G vs A (OR)	95% CI	P	I²(%)*	AG vs AA (OR)	95% CI	P	I²(%)*	GG vs AA (OR)	95% CI	P	I²(%)*	AG+GG vs AA (OR)	95% CI	P	I²(%)*	GG vs AA+AG (OR)	95% CI	P	I²(%)*
Total	7	1.12	0.98–1.28	.11	61.8	1.13	1.00–1.29	.05	37.5	1.26	0.94–1.69	.13	64.3	1.18	0.97–1.43	.09	55.0	1.14	0.92–1.41	.25	50.5
HWE-yes	6	1.11	0.95–1.30	.19	67.6	1.19	0.98–1.43	.07	40.7	1.23	0.87–1.72	.24	68.5	1.21	0.97–1.51	.10	61.8	1.08	0.86–1.35	.51	46.9
Ethnicity																					
Asian	5	1.02	0.92–1.13	.74	0	1.04	0.88–1.22	.67	0	1.03	0.83–1.27	.82	10.8	1.03	0.89–1.21	.68	0	1.01	0.83–1.22	.93	26.6
Caucasian	2	1.37	0.91–2.05	.13	85.2	1.46	0.90–2.38	.13	68.7	1.93	0.79–4.72	.15	86.6	1.61	0.87–2.99	.13	81.6	1.44	0.85–2.44	.18	76.3
Design																					
PB	5	1.16	0.99–1.36	.06	62.4	1.15	1.00–1.33	.05	36.0	1.38	0.97–1.95	.07	65.8	1.21	0.97–1.50	.09	55.3	1.24	0.96–1.60	.10	51.5
HB	2	1.00	0.78–1.29	.97	46.0	1.20	0.69–2.09	.52	68.2	0.91	0.66–1.25	.57	12.6	1.15	0.67–2.00	.61	70.0	0.88	0.67–1.16	.38	0
Type																					
NPC	2	1.33	0.80–2.19	.27	85.6	1.45	0.81–2.58	.21	68.8	1.80	0.59–5.45	.31	86.5	1.55	0.74–3.24	.24	82.4	1.39	0.69–2.79	.36	75.8
OC	3	1.05	0.88–1.27	.57	44.1	1.06	0.79–1.42	.69	42.6	1.14	0.75–1.72	.55	51.2	1.07	0.82–1.41	.61	41.0	1.09	0.73–1.64	.68	60.0

Fas -1377G>A

Locus	N*	A vs G (OR)	95% CI	P	I²(%)*	GA vs GG (OR)	95% CI	P	I²(%)*	AA vs GG (OR)	95% CI	P	I²(%)*	GA+AA vs GG (OR)	95% CI	P	I²(%)*	AA vs GG+GA (OR)	95% CI	P	I²(%)*
Total	7	1.09	1.00–1.19	.05	—	1.00	0.89–1.13	.97	0	1.24	0.92–1.67	.16	0	1.05	0.94–1.17	.42	47.0	1.21	0.90–1.63	.20	53.4
HWE-yes	6	1.09	1.00–1.19	.04	—	0.99	0.87–1.12	.85	0	1.30	0.96–1.76	.09	0	1.04	0.93–1.17	.49	48.0	1.28	0.95–1.72	.11	53.0
Ethnicity																					
Asian	5	1.12	1.01–1.23	.03	—	1.06	0.92–1.23	.40	36.0	1.14	0.81–1.60	.45	0	1.10	0.96–1.26	.17	55.9	1.10	0.80–1.54	.54	61.6
Caucasian	2	1.01	0.84–1.21	.94	—	0.89	0.72–1.09	.25	0	1.91	1.02–3.54	.04	0	0.84	0.77–1.15	.57	0	1.96	1.05–3.63	.03	0
Design																					
PB	5	1.06	0.92–1.23	.39	—	0.97	0.85–1.12	.71	47.7	1.29	0.88–1.91	.19	0	1.03	0.91–1.18	.64	58.4	1.27	0.87–1.86	.21	62.4
HB	2	1.08	0.90–1.29	.39	—	1.09	0.86–1.39	.47	0.0	1.15	0.75–1.76	.52	0	1.10	0.87–1.38	.42	25.0	1.03	0.55–1.92	.92	41.2
Type																					
OS	3	1.10	0.96–1.26	.18	—	1.07	0.88–1.31	.48	0	1.23	0.90–1.68	.20	0	1.10	0.91–1.33	.32	0	1.21	0.90–1.61	.21	0

FasL -844C>T

Locus	N*	T vs C (OR)	95% CI	P	I²(%)*	CT vs CC (OR)	95% CI	P	I²(%)*	TT vs CC (OR)	95% CI	P	I²(%)*	CT+TT vs CC (OR)	95% CI	P	I²(%)*	TT vs CC+CT (OR)	95% CI	P	I²(%)*
Total	6	0.91	0.81–1.04	.16	46.2	0.89	0.79–1.00	.05	38.3	0.85	0.65–1.10	.22	0	0.88	0.79–0.98	.02	35.8	0.92	0.70–1.21	.54	60.9
HWE-yes	4	0.92	0.74–1.15	.49	49.1	0.92	0.71–1.18	.49	54.4	0.78	0.53–1.15	.51	0	0.90	0.69–1.16	.40	60.5	0.85	0.57–1.27	.43	63.5
HWE-no	4	0.91	0.80–1.03	.14	63.5	0.84	0.70–1.02	.07	0	0.96	0.61–1.52	.86	0	0.86	0.72–1.02	.08	0	1.03	0.60–1.77	.91	77.0
Ethnicity																					
Asian	5	0.92	0.77–1.09	.32	56.7	0.87	0.76–1.01	.06	49.0	0.86	0.60–1.23	.39	0	0.86	0.75–0.99	.04	47.7	0.93	0.64–1.35	.69	68.1
Design																					
PB	5	0.89	0.76–1.03	.11	57.2	0.88	0.77–1.00	.05	62.0	0.80	0.55–1.16	.24	0	0.87	0.77–0.98	.02	58.3	0.84	0.58–1.23	.38	61.3
HB	2	1.03	0.70–1.50	.89	55.3	0.94	0.72–1.24	.66	0	0.96	0.55–1.68	.89	0	0.91	0.71–1.18	.48	0	1.07	0.57–1.99	.84	79.5
Type																					
OS	3	1.00	0.82–1.23	.99	18.7	1.05	0.85–1.30	.64	0	0.86	0.62–1.19	.36	0	1.00	0.82–1.21	.98	0	0.94	0.60–1.47	.78	66.0

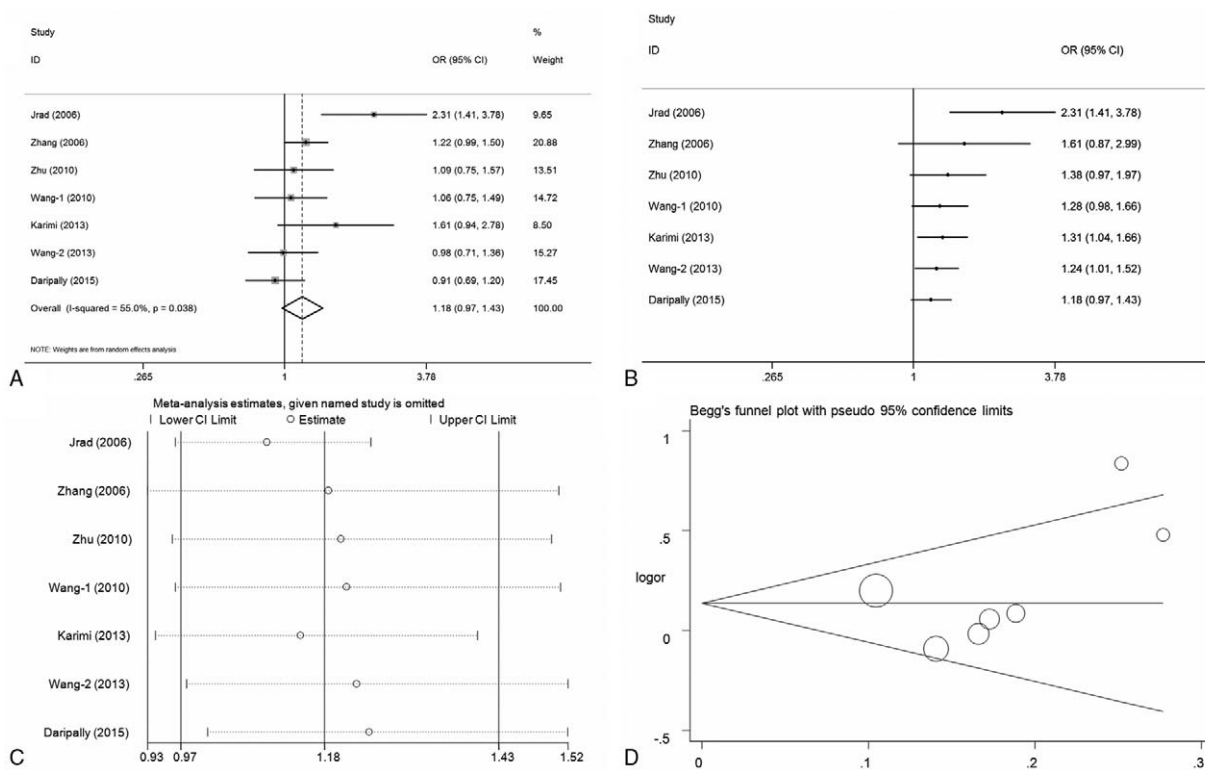HB = hospital-based, PB = population-based.
* Numbers of comparisons.

Figure 2. Statistical analysis of the association between Fas -670A>G polymorphism and head and neck cancer risk in the AG+GG versus AA model. (A) ORs and 95% CIs; (B) cumulative analysis; (C) sensitivity analysis; (D) publication bias.

except a marginally increased cancer risk (AG vs AA: OR = 1.13, 95% CI = 1.00–1.29, P = .05, I^2 = 37.5%) (Table 2). Heterogeneities were identified in allele contrast (G vs A), codominant models (GG vs AA), dominant model (AG+GG vs AA), and recessive model (GG vs AA+AG). Meta-regression analyses revealed no remarkable factors contributing to these heterogeneities. Stratified analyses revealed the heterogeneities in Asian population alleviate remarkable. Moreover, no significant association was demonstrated in the subgroup analyses based on HWE status, ethnicity difference, control design, and cancer type (Table 2). Cumulative analyses by publication date revealed apparent change from significant cancer risk to negative association with the new studies were added (Fig. 2B for AG +GG vs AA model). Furthermore, sensitivity analysis indicated a slight risk of HNC when the study of Daripally et al[39] was omitted (Fig. 2C for AG+GG vs AA model). Finally, funnel plot was used and Egger test was performed to estimate the publication bias between the included studies and did not identify any asymmetrical evidence (Fig. 2D for AG+GG vs AA model). The results were further supported by Egger test (G vs A: P = .55; AG vs AA: P = .30; GG vs AA: P = .56; AG+GG vs AA: P = .30; GG vs AA+AG: P = .81).

3.2.2. Fas -1377G>A polymorphism and HNC risk. Seven case–control studies involving 2666 cases and 3582 controls focused on the association between the Fas -1377G>A polymorphism and HNC risk. Overall, only a marginally increased risk was identified in the allele contrast (A vs G: OR = 1.09, 95% CI = 1.00–1.19, P = .05, I^2 = 23.0%; GA vs GG: OR = 1.00, 95% CI = 0.89–1.13, P = .97, I^2 = 0%; AA vs GG: OR = 1.24, 95% CI = 0.92–1.67, P = 0.16, I^2 = 47.0%; GA+AA vs GG: OR = 1.05, 95% CI = 0.94–1.17, P = .42, I^2 = 0%; AA vs GG

+GA: OR = 1.21, 95% CI = 0.90–1.63, P = .20, I^2 = 53.4%) (Table 2, Fig. 3A for GA+AA vs GG model). Heterogeneities were revealed in codominant models (AA vs GG) and the recessive model (GG vs AA+AG). Meta-regression analyses did not identify any remarkable factors contributing to these heterogeneities. Stratified analyses demonstrated that the heterogeneities were markedly alleviated in a Caucasian population or hospital control studies. Moreover, no significant association was identified in any subgroup analyses based on HWE status, ethnicity difference, control design, and cancer type (Table 2). Cumulative analyses by publication date revealed a negative association with the new studies added in stages. Furthermore, sensitivity analysis indicated that the results were not stable without certain studies in the allele contrast (A vs G), codominant models (AA vs GG), and recessive model (GG vs AA+AG) (Fig. 3C for GA+AA vs GG model). Finally, funnel plot was used and Egger test was performed to estimate the publication bias between the included studies, and did not identify asymmetrical evidence. The results were further supported by Egger test (A vs G: P = .10; GA vs GG: P = .66; AA vs GG: P = .48; GA+AA vs GG: P = .70; AA vs GG+GA: P = .46) (Fig. 3D for GA+AA vs GG model).

3.2.3. FasL -844C>T polymorphism and HNC risk. In total, 6 case–control studies with 2524 cases and 3083 controls focused on the association between the FasL -844C>T polymorphism and HNC risk. Overall, a significant association of protective effect was detected between the FasL -844C>T polymorphism and HNC risk in codominant models (CT vs CC: OR = 0.89, 95% CI = 0.79–1.00, P = .05, I^2 = 38.3%) and the dominant model (CT+TT vs CC: OR = 0.88, 95% CI = 0.79–0.98, P = .02, I^2 = 35.8%) (Table 2, Fig. 4A for CT+TT vs CC model).
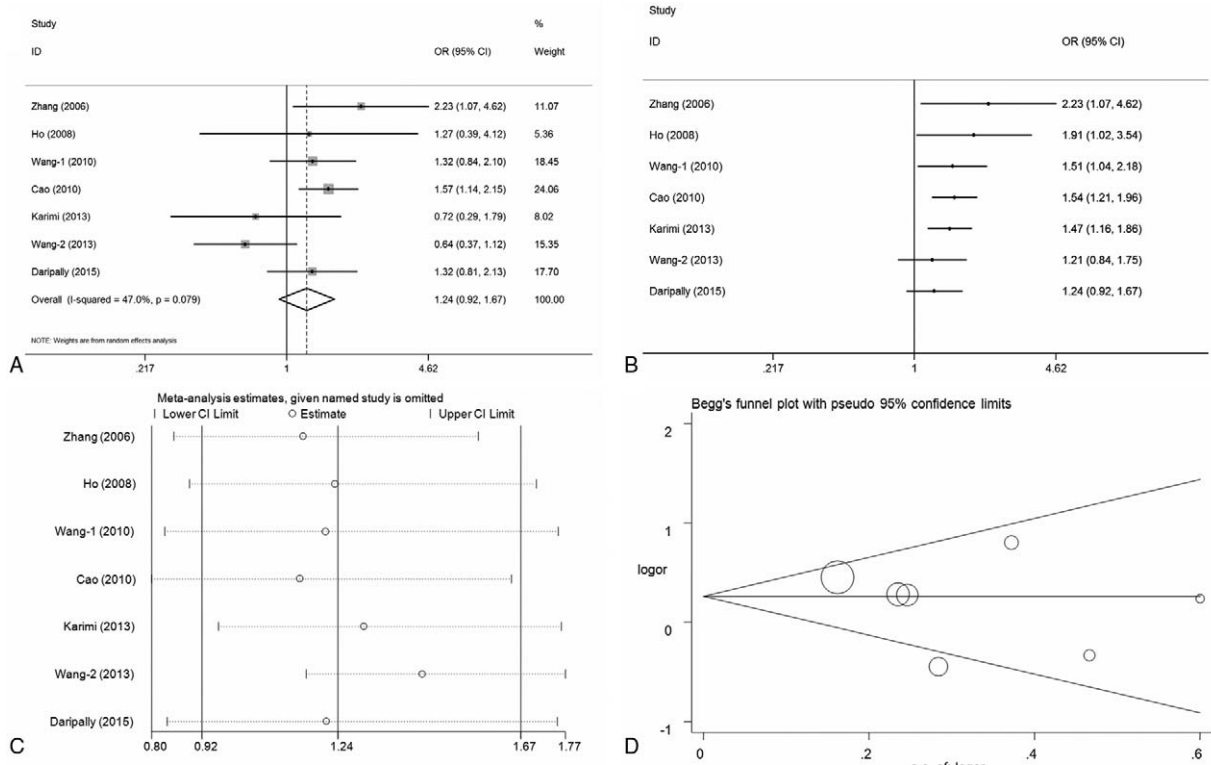
Figure 3. Statistical analysis of the association between Fas -1377G>A polymorphism and head and neck cancer risk in the GA+AA versus GG model. (A) ORs and 95% CIs; (B) cumulative analysis; (C) sensitivity analysis; (D) publication bias.
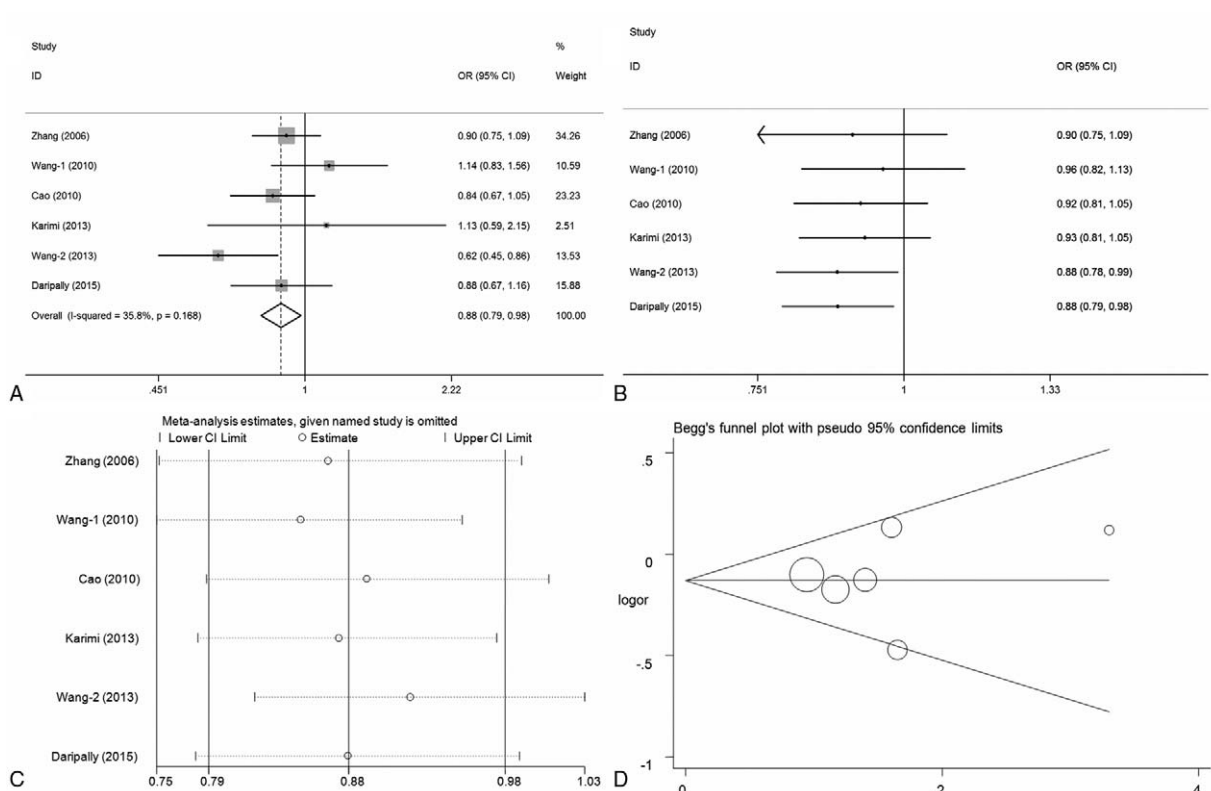

Figure 4. Statistical analysis of the association between FasL -844C>T polymorphism and head and neck cancer risk in the CT+TT versus CC model. (A) ORs and 95% CIs; (B) cumulative analysis; (C) sensitivity analysis; (D) publication bias.

Heterogeneities were identified in allele contrast (T vs C), codominant models (TT vs CC), and recessive model (TT vs CC +CT). Meta-regression analyses did not identify any remarkable factors contributing to these heterogeneities. Subgroup analyses revealed certain decreased cancer risks in Asian populations (CT +TT vs CC: OR = 0.86, 95% CI = 0.75–0.99, P = .04, I^2 = 47.7%) and population-based controls study (CT+TT vs CC: OR = 0.87, 95% CI = 0.77–0.98, P = .02, I^2 = 58.3%) (Table 2). Cumulative analyses by publication date demonstrated significant alterations in results when the study by Wang et al[38] was added in the codominant model (CT vs CC) and dominant model (CT+TT vs CC) (Fig. 4B for CT+TT vs CC model). Furthermore, sensitivity analysis indicated that the results were not stable when the studies were omitted one by one (Fig. 4C for CT+TT vs CC model). In addition, funnel plot was used and Egger test was performed to estimate the publication bias between the included studies and did not identify any asymmetrical evidence. The results were further supported by Egger test (T vs C: P = .71; CT vs CC: P = .98; TT vs CC: P = 1.00; CT+TT vs CC: P = .83; TT vs CC+CT: P = .97) (Fig. 4D for CT+TT vs CC model).

4. Discussion

Apoptosis plays a critical role during the procedure of cancer development.[40] The *Fas/FasL* genes encode important cytokines in the regulation of apoptotic cell death, and the dysregulation of theses cytokines has been revealed to induce cancer cell immune evasion and tumorigenesis.[41,42] Numerous studies have suggested that the decreased expression level of the *Fas* gene may protect tumor cells against programmed cell death by down-regulating immune responses, and the increased expression of the *FASL* gene may have a similar effect by increasing the resistance ability of tumor cells.[21,42]

Today, Fas -670A>G (rs1800682), Fas -1377G>A (rs2234767), and FasL -844C>T (rs763110) are the most common single SNPs. These mutations are located in the promoter region and alter Fas/FasL transcription and expression, which results in abnormal cell apoptosis and cancer development.[43,44] Some published molecular epidemiological studies have demonstrated the association between *Fas/FasL* gene polymorphisms and many types of cancer risk, such as esophageal cancer,[45] gastric cancer,[46] lung cancer,[47] and breast cancer.[48] For the Fas -670A>G polymorphism, Bel Hadj Jrad et al[24] reported a significantly increased risk of nasopharyngeal cancer in carriers of the heterozygote (OR = 2.0, 95% CI = 1.19–3.33) and homozygote (OR = 3.19, 95% CI = 1.76–5.77) variants in 2006. Moreover, similarly increased risks were also observed in other studies, together with a negative association between the Fas -670A>G polymorphism and HNC risk. This trend inconsistent results between the FAS -1377G>A and FASL -844C>T polymorphisms and HNC risk also exist in published case–controls studies, which may be due to the limited researches and small sample sizes.

In this meta-analysis, we investigated the associations between the Fas -670A>G, Fas -1377G>A, and FasL -844C>T polymorphisms and HNC susceptibility, on the basis of 9 published studies. The pooled results indicated that the FasL -844C>T polymorphism may serve a protective function role against HNC development. In the subgroup analysis based on ethnic diversity and control design, the protective effects were also observed in an Asian population and population-based controls. As we know, HNC always originate from the malignant transformation of normal epithelial cells in the upper aerodigestive tract. Some

damage stimulations, including the alcohol, cigarette, virus infection, and traumatic ulcers, have always existed, which could influence the normal procession of cell cycle and trigger the growth of tumorous. FasL is an important transmembrane protein that belongs to TNF family. In immune system, the complex of Fas/FasL binding plays a fundamental role to induce the producer of cell apoptosis. FasL-844T C>T (rs763110) is the most important polymorphism located in the promoter region. This mutation may change the expression of FasL protein, influence the capacity to combine with the FAS, and accelerate the apoptosis process of cancer cells and against head and neck tumorigenesis. For the Fas -670A>G and Fas -1377G>A polymorphisms, only 1 genetic model demonstrated a marginally increased risk of HNC, which revealed no significant association between the 2 Fas polymorphisms and HNC risk based on the current evidences.

To our knowledge, this is the first quantitative assessment investigating the association between *Fas/FasL* gene polymorphisms and HNC risk. Nine publications involving 3179 HNC patients and 4217 controls were included. The current study has its limitations, but we think that these quantitative results may help us to gain a more precise understanding regarding the association between *Fas/FasL* gene polymorphisms and HNC risk. First, all 5 analysis comparison patterns were performed, and the subgroup analyses were conducted to investigate the potential association comprehensively. Second, Egger test and Begg funnel plots demonstrated that no publication bias existed in each locus. Finally, a more scientific retrieval strategy was used in our meta-analysis, which would help to further include relevant studies.

Furthermore, certain limitations of this meta-analysis should to mentioned. First, there were only 7, 7, and 6 independent case–control studies for the Fas -670A>G, Fas -1377G>A, and FasL -844C>T polymorphisms, respectively. The reliability and authenticity of our results may be influenced by the limited number of studies and small sample sizes. Second, other risk factors, including drinking and smoking, were not analyzed owing to the information deficiency in the included studies. The interactions between genetic mutation and environmental factors could not be explained in this research. Third, the research subjects of the included studies were of Asian and Caucasian origins. Thus, the bias of racial diversity could not be avoided and the results are not applicable to all populations. Fourth, moderate heterogeneity existed in some genetic models for the Fas -670A>G, and FasL -844C>T polymorphisms. And the subsequent meta-regression could not identify any interfering factors contributing to heterogeneity. Finally, certain HWE deviations were revealed in the distributions of controls in some included studies, which may be due to the small sample size or other experimental technique errors in the study.

Despite these limitations, this meta-analysis indicated that the FasL -844C>T polymorphism maybe a protective factor against HNC development; however, the Fas -670A>G and Fas -1377G>A polymorphisms were not associated with HNC risk. More case–control studies investigating patients of other races and larger patient cohorts are required to support the findings of this study.

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