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CD95 rs1800682A/G Variant and Tumor Risk in Asians: Evidence from a Meta-Analysis of 36 Case-Control Studies Containing 22 438 Samples

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Data Interpretation D
Manuscript Preparation E
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Background: The CD95 gene plays a key role in regulating cell growth and tumor genesis. To date, several publications have focused on the CD95 rs1800682A/G site polymorphism and various types of tumors in Asians; however, this association is still controversial and obscure. Therefore, a meta-analysis combined with all publications to clarify this association is necessary.

Material/Methods: A search in the PubMed and SinoMed databases was performed to detect all relevant included publications. Odds ratio (OR) and 95% confidence intervals (CI) revealed association strengths.

Results: Overall, 36 case-control studies were chosen based on the search criteria. There was no association of the CD95 rs1800682A/G site polymorphism with tumor risk in total and ethnicity subgroup analysis. However, further stratified analysis in the cancer subgroup revealed weakly significant associations in hepatocellular carcinoma (AA+AG vs. GG: OR=0.93, 95% CI=0.87–0.99, $P=0.035$; AG vs. GG: OR=0.89, 95% CI=0.80–0.99, $P=0.036$).

Conclusions: The CD95 rs1800682A/G site polymorphism may be associated with hepatocellular carcinoma susceptibility. Further large-scale and well-designed studies regarding tumor types and ethnicities are still required to confirm our results.

MeSH Keywords: **Antigens, CD95 • Carcinoma, Hepatocellular • DNA Copy Number Variations • Meta-Analysis**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/892547>

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Background

CD95 (also known as TNFRSF6/Fas/APO-1), is a cell surface receptor and plays a key role in apoptotic signaling pathway in a variety of cell types [1,2]. The CD95 gene is located at chromosome 10q24.1, consisting of 9 exons and 8 introns. One of the single-nucleotide polymorphisms (SNPs) has been widely reported in the promoter region. An A to G transition at nucleotide position -670 (rs1800682), located within the signal transducer and activator of transcription (STAT-1), may influence CD95 expression and deregulate cell death signaling, which could contribute to carcinogenesis [3,4].

Many epidemiologic studies on CD95 rs1800682A/G polymorphism and tumor susceptibility have been reported. However, conclusions across these studies were inconsistent. Considering the vital role of CD95 rs1800682A/G polymorphism in cancer (influencing the CD95 gene expression may lead to tumorigenesis), all eligible case-control studies were identified and selected in our present meta-analysis.

Material and Methods

Retrieval of studies and selection criteria

We systematically searched available studies updated on 1 June 2014 in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and SinoMed (<http://sinomed.imicams.ac.cn>) databases. Keywords contained 'CD95 or Fas or TNFRSF6 or APO-1', 'cancer or tumor', 'polymorphism or variant'. The inclusion criteria were: (1) case-control study about CD95 rs1800682A/G polymorphism in tumor about Asians; (2) information on each genotype (AA, AG, and GG) in both case and control group. Exclusion criteria were: (1) no control group; (2) insufficient genotype frequency data; (3) reduplicate studies, and (4) study not to accord with Hardy-Weinberg equilibrium (HWE) of controls.

Data extraction

Extracted data included: first author's last name, publication year, original country, race, cancer category, genotype distribution, and HWE of controls. If 1 tumor was only reported in 1 article, it was placed into the 'other cancer' subgroup.

SNP genotyping

Genotyping for CD95 rs1800682A/G polymorphism was analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), ligase detection reaction-polymerase chain reaction (LDR-PCR), Tetra-amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR), and TaqMan technology.

Quality score assessment

The Newcastle-Ottawa Scale [5] was selected to assess the quality of each study. This measure assesses aspects of methodology in observational studies related to study quality, including selection of cases, comparability of populations, and ascertainment of exposure to risks. The NOS ranges from zero (worst) to 9 stars (best). Studies with a score of 7 stars or greater were considered as high quality.

Statistical analysis

All the statistical analysis was performed by Stata software (Version 10.0; StataCorp LP, College Station, TX). Odds ratio (OR) and 95% confidence intervals (CI) were used to assess the strength of the association between the CD95 rs1800682A/G polymorphism and tumor risk. The statistical significance of the summary OR was determined with the Z-test. A heterogeneity assumption was evaluated among studies using the chi-square-based Q-test. When heterogeneity was more than 0.10, Mantel-Haenszel method (fixed-effects model) was used to calculate the pooled OR. Otherwise, DerSimonian and Laird method (random-effects model) was performed [6,7]. The departure of the CD95 rs1800682A/G polymorphism from expected frequencies under HWE was assessed in controls using the Pearson chi-square test. Sensitivity analysis was performed by limiting the meta-analysis to high-quality studies (according to the NOS score). In addition, publication bias was assessed by funnel plots and evaluated by both Egger's and Begg's test, respectively. A $P < 0.05$ for Egger's test or Begg's test indicates the presence of potential publication bias [8,9].

Results

Eligible studies and including characteristics

A total of 217 studies were found in the PubMed (213 articles) and SinoMed (4 articles) databases using keywords. After reviewing the titles and abstracts, 129 articles were excluded; 34 were removed mainly because they were duplications, reviews, clinical trials, letters or comments, meta-analyses, or investigated other site polymorphisms in CD95 or CD95L genes. Subsequently, the remaining 54 publications were further evaluated for eligibility, including 36 case-control studies in Asian populations. The HWE in control group in 3 publications, which were excluded, was not meet with selection criteria. Moreover, the ethnicity of 2 articles was African and mixed, which were also excluded because just 1 paper cannot be combined in meta-analysis. Finally, 34 articles including 36 case-control studies [10–43] were included in the present meta-analysis. The detailed flow chart of study selection is shown in Figure 1. Study characteristics for the association between CD95 rs1800682A/G

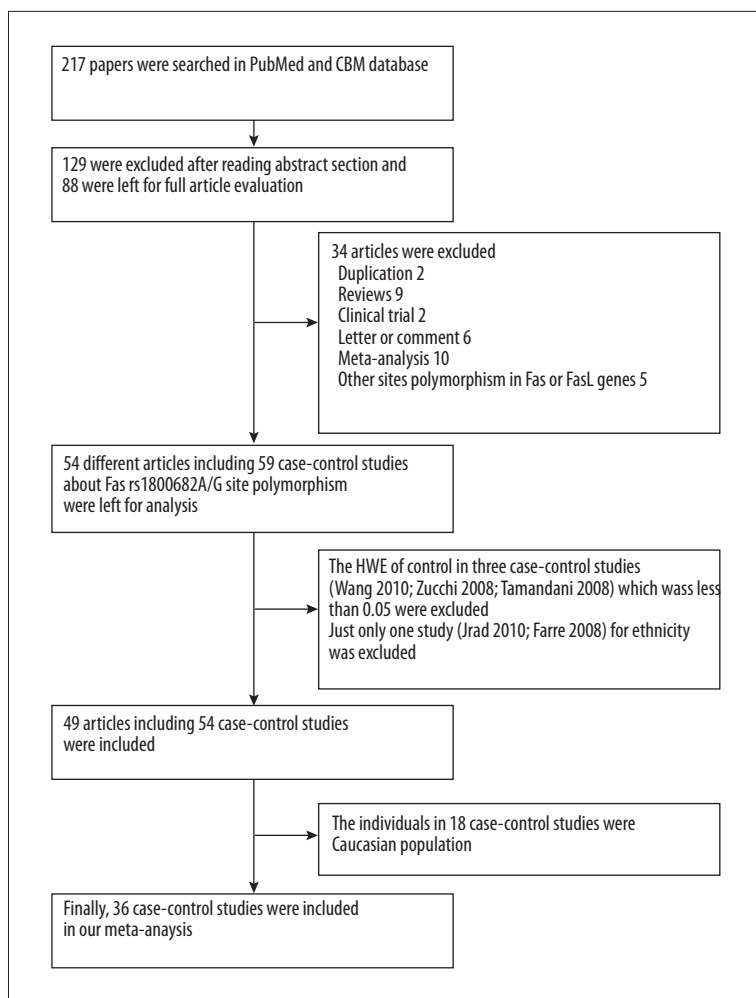


Figure 1. Flowchart illustrating the search strategy for CD95 rs1800682A/G polymorphism and cancer risk in Asians.

and tumor risk in Asians are summarized in Table 1. The NOS results show that the average score was 7.08, which indicated that the methodological quality was generally good (Table 2).

Pooled analysis

The results of the quantitative synthesis of the data are summarized in Table 3. In the total analysis, there was no association between the CD95 rs1800682A/G polymorphism and whole tumor risk: OR=1.04, 95% CI=0.97–1.12, $P_{\text{heterogeneity}}=0.010$ (random model) for AA vs. AG+GG, OR=1.01, 95% CI=0.91–1.13, $P_{\text{heterogeneity}}=0.015$ (random model) for AA vs. GG and OR=0.98, 95% CI=0.89–1.07, $P_{\text{heterogeneity}}=0.049$ (random model) for AA+AG vs. GG, OR=1.01, 95% CI=0.96–1.07, $P_{\text{heterogeneity}}=0.005$ (random model) for A-allele vs. G-allele, OR=0.99, 95% CI=0.97–1.01, $P_{\text{heterogeneity}}=0.049$ (random model) for AG vs. GG. At the same time, no relationship was detected among this SNP and source of control group.

In the subgroup study by the type of cancer, a weak association was found between CD95 rs1800682A/G polymorphism

and hepatocellular carcinoma [OR: 0.93, 95% CI: 0.87–0.99, $P=0.521$ for heterogeneity (fixed model) and $P=0.035$ in dominant model, Figure 2; OR: 0.89, 95% CI: 0.80–0.99, $P=0.506$ for heterogeneity (fixed model) and $P=0.036$ in heterozygote comparison model (Figure 3). No association was found in other types of cancer, such as breast cancer, lung cancer, breast cancer, gastric cancer, or cervical cancer.

Sensitivity analysis and publication bias

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. The included studies were limited to those with high NOS score. For CD95 rs1800682A/G polymorphism, 7 studies with relatively low NOS score (<7) [19,27,28,31,34,40,42] were excluded from the sensitivity analysis. The corresponding pooled ORs were not materially altered. The above results of sensitivity analyses indicated that the overall results were statistically robust. The results of sensitivity analyses are shown in Table 2. The publication bias was assessed by Begg’s funnel plots and Egger’s linear

Table 1. Characteristics of all included studies about CD95 rs1800682A/G site polymorphism and cancer risk in Asians.

First author-Span (month/year)	Country	Cancer type	Source of control	Cases AA/AG/GG	Controls AA/AG/GG	HWE
Gangwar-(May/2004 to June/2008)	India	Bladder cancer	HB	70/94/48	79/129/42	0.384
Li-(January/2003 to November/2004)	China	Bladder cancer	HB	78/119/19	96/124/32	0.409
Chang-(September/2010 to December/2011)	China	Bladder cancer	HB	61/92/21	77/103/30	0.636
Zhang-(June/1997 to March/2004)	China	Breast cancer	PB	320/393/123	321/390/123	0.797
Hashemi-(NA)	Iran	Breast cancer	PB	55/55/24	63/78/23	0.884
Li-(January/2001 to March/2004)	China	Cervical cancer	PB	138/144/32	268/272/75	0.641
Kang-(April/1996 to July/2002)	Korea	Cervical cancer	HB	48/73/33	53/84/23	0.264
Lai-(NA/1993 to NA/2000)	China-Taiwan	Cervical cancer	HB	121/137/60	91/161/66	0.736
Ueda-(NA)	Japan	Cervical cancer	HB	15/38/30	23/54/18	0.172
Sun-(June/2001 to March/2002)	China	Cervical cancer	PB	138/144/32	268/272/75	0.641
Lai-(NA/1993 to NA/2000)	China-Taiwan	Cervical cancer	HB	68/81/27	44/93/39	0.444
Ueda-(NA)	Japan	Endometrial cancer	HB	39/50/19	23/54/18	0.172
Chen-(February/2005 to October/2007)	China	Esophageal cancer	PB	82/84/22	130/158/36	0.242
Jain-(January/2003 to September/2005)	India	Esophageal cancer	PB	57/78/16	66/107/28	0.140
Sun-(July/1999 to December/2001)	China	Esophageal cancer	PB	224/247/117	246/321/81	0.130
Hu-(November/2008 to January 2010)	China	Gastric cancer	HB	54/61/14	28/47/20	0.973
Zhou-(NA/2003 to NA/2006)	China	Gastric cancer	PB	105/121/36	186/266/72	0.133
Wang-(July/2003 to April/2005)	China	Gastric cancer	PB	116/172/44	132/148/44	0.806
Hsu-(NA)	China-Taiwan	Gastric cancer	PB	25/47/14	33/48/20	0.736
Ikehara-(February/2001 to December/2003)	Japan	Gastric cancer	HB	62/141/68	71/130/70	0.504
Zhang-(March/2005 to March/2006)	China	Hepatocellular carcinoma	HB	9/27/9	21//11/4	0.200
Jung-(January/2001 to August/2003)	Korea	Hepatocellular carcinoma	PB	98/140/74	93/168/67	0.576
Kim-(NA)	Korea	Hepatocellular carcinoma	PB	30/41/28	78/118/44	0.957
Wang-(October/2009 to February/2011)	China	Larynx and hypopharynx carcinoma	PB	124/140/37	122/136/41	0.752
Kim-(January/1995 to June/2006)	Korea	Leukemia	PB	168/307/117	251/421/186	0.704
Tong-(January/2007 to NA/2011)	China	Leukemia	PB	157/159/45	198/255/66	0.249
Valibeigi-(NA/2008 to NA/2011)	Iran	Leukemia	HB	44/77/21	47/57/13	0.487
Park-(January/2001 to June/2002)	Korea	Lung cancer	HB	185/278/119	162/307/113	0.132
Zhu-(June/2008 to April/2009)	China	Nasopharyngeal carcinoma	HB	79/124/34	93/132/39	0.478
Han-(NA)	China	Neuroblastoma	PB	67/104/32	163/197/51	0.471
Ueda-(NA)	Japan	Ovarian cancer	HB	18/37/13	23/54/18	0.172
Li-(December/2002 to December/2010)	China	Ovarian cancer	PB	142/164/36	131/169/44	0.357
Yang-(NA)	China	Pancreatic cancer	PB	158/182/57	357/419/131	0.653
Mandal-(January/2007 to June/2009)	India	Prostate cancer	HB	57/103/32	74/116/34	0.296
Shao-(September/2003 to January/2010)	China	Prostate cancer	HB	238/274/90	228/351/124	0.579
Zhu-(July/2006 to NA/2009)	China	Renal cell carcinoma	HB	132/163/58	144/169/52	0.831

Table 2. Total and subgroup analysis about CD95 rs1800682A/G site polymorphism and cancer risk in Asians.

Variables	N	Cases/ controls	Dominant genetic model (AA+AG vs. GG)			Homozygote comparison (AA vs. GG)			Recessive genetic model (AA vs. AG+GG)		
			OR (95%CI)	Pb	P	OR (95%CI)	Pb	P	OR (95%CI)	Pb	P
Total	36	9874/12564	0.98 (0.89–1.07)	0.049	0.599	1.01 (0.91–1.13)	0.015	0.781	1.04 (0.97–1.12)	0.010	0.268
Cancer type											
Bladder cancer	3	602/712	1.05 (0.64–1.70)	0.096	0.855	1.01 (0.91–1.11)	0.383	0.923	0.98 (0.85–1.14)	0.846	0.797
Breast cancer	2	970/998	0.99 (0.96–1.03)	0.397	0.731	0.99 (0.92–1.07)	0.641	0.822	1.01 (0.90–1.12)	0.646	0.922
Cervical cancer	6	1359/1979	0.98 (0.71–1.38)	0.019	0.930	1.10 (0.75–1.63)	0.012	0.619	1.15 (0.91–1.46)	0.038	0.252
Esophageal cancer	3	927/1173	0.85 (0.50–1.44)	0.037	0.545	0.93 (0.55–1.56)	0.057	0.772	1.05 (0.94–1.17)	0.645	0.423
Gastric cancer	5	1080/1315	1.02 (0.98–1.06)	0.465	0.328	1.02 (0.95–1.11)	0.237	0.561	1.01 (0.77–1.32)	0.072	0.960
Hepatocellular carcinoma	3	456/604	0.93 (0.87–0.99)	0.521	0.035	0.62 (0.32–1.21)	0.073	0.161	0.67 (0.30–1.46)	0.002	0.303
Leukamia	3	1095/1494	1.01 (0.98–1.05)	0.467	0.602	1.01 (0.94–1.09)	0.310	0.771	0.98 (0.74–1.31)	0.083	0.914
Other cancer	7	2181/2923	0.99 (0.97–1.02)	0.912	0.534	0.99 (0.94–1.05)	0.602	0.849	1.01 (0.94–1.09)	0.211	0.800
Ovarian cancer	2	410/439	1.02 (0.97–1.08)	0.730	0.434	1.06 (0.95–1.19)	0.889	0.293	1.09 (0.92–1.30)	0.992	0.330
Prostate cancer	2	794/927	1.02 (0.98–1.06)	0.313	0.345	1.07 (0.98–1.18)	0.116	0.110	1.12 (0.71–1.75)	0.055	0.630
Source of control											
HB	18	4062/4308	0.99 (0.85–1.15)	0.077	0.888	1.04 (0.85–1.27)	0.004	0.732	1.05 (0.89–1.23)	0.000	0.561
PB	18	5812/8256	0.99 (0.98–1.01)	0.125	0.431	0.99 (0.97–1.02)	0.424	0.757	1.01 (0.97–1.06)	0.780	0.506
Sensitivity analysis	29	8759/11461	0.99 (0.98–1.01)	0.124	0.339	1.00 (0.97–1.02)	0.369	0.915	1.02 (0.98–1.06)	0.546	0.270
Variables	N	Cases/ controls	Allelic contrast (A-allele vs. G-allele)			Heterozygote comparison (AG vs. GG)					
			OR (95%CI)	Pb	P	OR (95%CI)	Pb	P			
Total	36	9874/12564	1.01(0.96-1.07)	0.005	0.664	0.99(0.97-1.01)	0.049	0.599			
Cancer type											
Bladder cancer	3	602/712	0.99 (0.93–1.06)	0.763	0.856	1.07 (0.60–1.91)	0.047	0.826			
Breast cancer	2	970/998	1.00 (0.95–1.05)	0.901	0.913	0.99 (0.93–1.05)	0.282	0.686			
Cervical cancer	6	1359/1979	1.05 (0.87–1.27)	0.007	0.620	0.93 (0.68–1.27)	0.064	0.658			
Esophageal cancer	3	927/1173	0.98 (0.94–1.03)	0.111	0.446	0.79 (0.46–1.33)	0.048	0.370			
Gastric cancer	5	1080/1315	1.01 (0.96–1.06)	0.121	0.637	1.03 (0.97–1.10)	0.599	0.268			
Hepatocellular carcinoma	3	456/604	0.73 (0.47–1.12)	0.014	0.153	0.89 (0.80–0.99)	0.506	0.036			
Leukamia	3	1095/1494	1.01 (0.96–1.06)	0.168	0.674	1.01 (0.96–1.07)	0.488	0.606			
Other cancer	7	2181/2923	1.00 (0.97–1.03)	0.440	0.878	0.98 (0.94–1.02)	0.940	0.417			
Ovarian cancer	2	410/439	1.04 (0.97–1.12)	0.825	0.286	1.02 (0.94–1.12)	0.693	0.599			
Prostate cancer	2	794/927	1.07 (0.80–1.45)	0.062	0.619	1.01 (0.94–1.08)	0.677	0.769			
Source of control											
HB	18	4062/4308	1.01 (0.91–1.12)	0.000	0.816	0.99 (0.96–1.02)	0.311	0.457			
PB	18	5812/8256	1.00 (0.98–1.02)	0.607	0.952	0.95 (0.83–1.08)	0.067	0.432			
Sensitivity analysis	29	8759/11461	1.00 (0.99–1.02)	0.417	0.795	0.94 (0.85–1.04)	0.084	0.240			

Table 3. Assessment of study quality.

Studies	Quality indicators from Newcastle-Ottawa Scale									Studies	Quality indicators from Newcastle-Ottawa Scale										
	1	2	3	4	5A	5B	6	7	8		Total	1	2	3	4	5A	5B	6	7	8	Total
Li/2006	*	*	/	*	*	*	*	*	/	VII*	Zhang/2007	*	*	*	*	*	/	*	*	/	VII*
Chang/2013	*	*	/	*	*	*	*	*	/	VII*	Hashemi/2013	*	*	*	*	*	/	*	*	/	VII*
Gangwar/2010	*	*	/	*	*	*	*	*	/	VII*	Li/2009	*	*	*	*	*	*	*	*	/	VIII*
Lai/2005	*	*	/	*	*	/	*	*	/	VI*	Sun/2004	*	*	*	*	*	*	*	*	/	VIII*
Lai/2003	*	*	/	/	*	/	*	*	/	V*	Chen/2009	*	*	*	*	*	*	*	*	/	VIII*
Ueda/2006	*	*	/	*	*	*	*	*	/	VII*	Sun/2005	*	*	*	*	*	*	*	*	/	VIII*
Kang/2008	*	*	/	*	*	/	*	*	/	VI*	Jain/2007	*	*	*	*	/	/	*	*	/	VI*
Hu/2011	*	*	/	*	*	/	*	*	/	VI*	Zhou/2010	*	*	*	*	*	*	*	*	/	VIII*
Ikehara/2006	*	*	/	*	*	*	*	*	/	VII*	Wang/2009	*	*	*	*	*	*	*	*	/	VIII*
Zhang/2009	*	*	/	*	*	/	*	*	/	VI*	Hsu/2008	*	*	*	*	*	*	*	*	/	VIII*
Valibeigi/2014	*	*	/	*	*	/	*	*	/	VI*	Jung/2007	*	*	*	/	*	*	*	*	/	VII*
Ueda/2006	*	*	/	*	*	*	*	*	/	VII*	Kim/2003	*	*	*	*	*		*	*	/	VII*
Park/2006	*	*	/	*	*	*	*	*	/	VII*	Tong/2012	*	*	*	*	*	*	*	*	/	VIII*
Zhu/2010	*	*	/	*	*	*	*	*	/	VII*	Kim/2010	*	*	*	*	*	*	*	*	/	VIII*
Zhu/2010	*	*	/	*	*	*	*	*	/	VII*	Wang/2013	*	*	*	*	*	*	*	*	/	VIII*
Ueda/2006	*	*	/	*	*	*	*	*	/	VII*	Han/2013	*	*	*	*		*	*	*	/	VII*
Shao/2011	*	*	/	*	*	*	*	*	/	VII*	Yang/2008	*	*	*	*	*	*	*	*	/	VIII*
Mandal/2012	*	*	/	*	*	*	*	*	/	VII*	Li/2013	*	*	*	*	*	/	*	*	/	VII*

1 – indicates cases independently validated; 2 – cases are representative of population; 3 – community controls; 4 – controls have no history of cancer disease; 5A – study controls for age; 5B – study controls for additional factor(s); 6 – ascertainment of exposure by blinded interview or record; 7 – same method of ascertainment used for cases and controls; 8 – nonresponse rate the same for cases and controls.

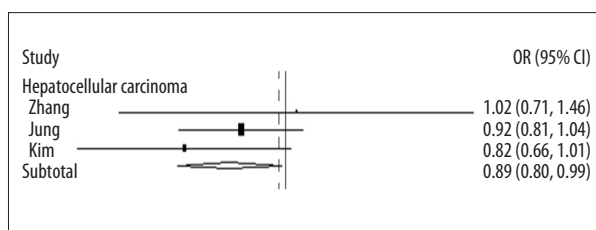


Figure 2. Forest plot of hepatocellular carcinoma risk associated with CD95 rs1800682A/G polymorphism (AA+AG vs. GG). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

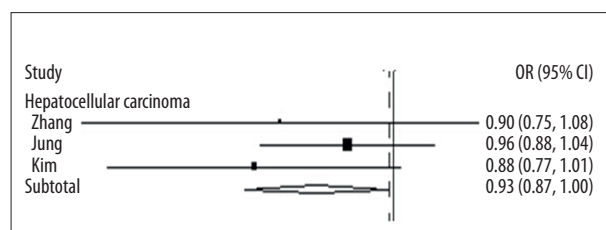


Figure 3. Forest plot of hepatocellular carcinoma risk associated with CD95 rs1800682A/G polymorphism (AG vs. GG). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

regression test. The shapes of the funnel plots did not reveal asymmetry (such as AA vs. GG: $t=0.21$, $P=0.836$; AA+AG vs. GG: $t=-0.20$, $P=0.841$, Figures 4 and 5). No statistically significant

difference was shown in the Egger's test, which indicated lack of publication bias in the whole analysis.

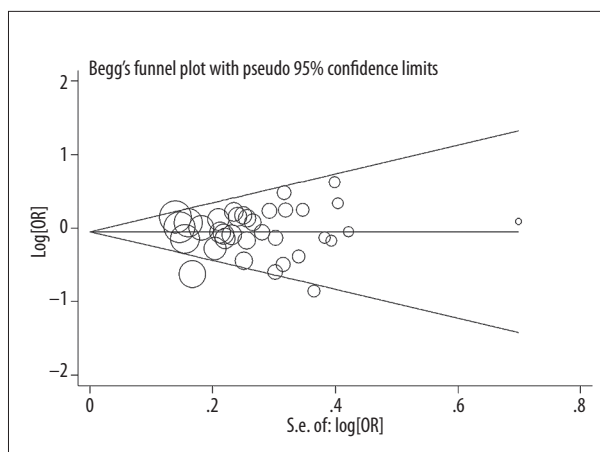


Figure 4. Begg's funnel plot for publication bias test (AG vs. GG). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line indicates mean effect size.

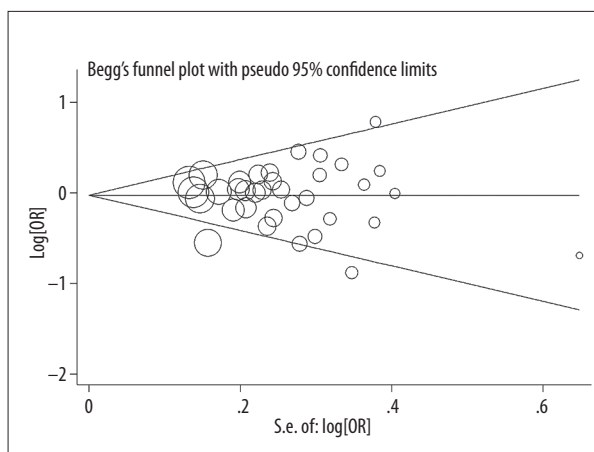


Figure 5. Begg's funnel plot for publication bias test (AA+AG vs. GG). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line indicates mean effect size.

Discussion

The global burden of cancer is increasing, with about 12.7 million cancer cases and 7.6 million cancer-related deaths each year [44]. Tumorigenesis is a multi-step and complex process interacting with various environmental and genetic factors. An abundance of evidence has established that gene polymorphisms play a vital role in individual susceptibilities to cancer, such as hepatocellular carcinoma [45–47]. Detection of functional gene polymorphisms, which are associated with cancer risk, may greatly improve cancer prevention and treatment.

The CD95/CD95L system induces the death signal cascade that subsequently results in cell apoptosis [48]. Decreased expression or mutation of CD95 gene has been detected in many types of malignant tumors, which not only impair the sensitivity of tumor cells to apoptotic signal, but also cause tumor cells to evade or weaken the immune elimination through the CD95-CD95L pathway [10]. Considering the important role of the CD95/CD95L system in the apoptotic process of cancer, and down-regulation of CD95 expression by rs1800682 A to G alteration, it is reasonable that CD95 rs1800682A/G polymorphism may affect cancer risk.

It is necessary to analyze associations between CD95 rs1800682A/G polymorphism and cancer risk through using meta-analysis to reach a credible and powerful conclusion. The present analysis is the first to combine all eligible studies, involving 9874 cancer cases and 12 564 controls in Asians. Our study found a weak positive association between CD95

rs1800682A/G and hepatocellular carcinoma, but no association was found with other cancers. There are 2 possible explanations for this phenomenon. On the one hand, cancer is a multifactorial disease because complicated interactions between several genetic and environmental factors may influence the development of cancer. On the other hand, no single gene or single environmental factor determines cancer risk [49].

For better interpreting the results, 2 potential limitations of our meta-analysis should be considered. First the sample size in most of the included studies was small, which may increase the probability of false-positives or false-negatives. Secondly, gene-gene and gene-environment interactions and other covariates, such as age, sex, family history, and lifestyle, should be reported and re-analyzed, because the expression of 1 gene may be influenced by other genes or environment factors.

Conclusions

Our analysis found a weak association between CD95 rs1800682A/G polymorphism and hepatocellular carcinoma risk in Asians. Well-designed studies with larger sample sizes and including gene-gene and gene-environment factors are needed to explain and confirm our findings.

Conflict of interest statement

None.

References:

1. Nagata S: Apoptosis by death factor. *Cell*, 1997; 88: 355–65
2. Los M, Van de Craen M, Penning LC et al: Requirement of an ICE/CED-3 protease for Fas/APO-1-mediated apoptosis. *Nature*, 1995; 375: 81–83

3. Huang QR, Morris D, Manolios N: Identification and characterization of polymorphisms in the promoter region of the human Apo-1/Fas (CD95) gene. *Mol Immunol*, 1997; 34: 577–82
4. Sibley K, Rollinson S, Allan JM et al: Functional FAS promoter polymorphisms are associated with increased risk of acute myeloid leukemia. *Cancer Res*, 2003; 63: 4327–30
5. Wells GA, Shea B, O'Connell D et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Health Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed Oct 20, 2011).
6. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, 1959; 22: 719–48
7. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials*, 1986; 7: 177–88
8. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics*, 1994; 50: 1088–101
9. Egger M, Davey Smith G, Schneider M et al: Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 1997; 315: 629–34
10. Han W, Zhou Y, Zhong R et al: Functional polymorphisms in FAS/FASL system increase the risk of neuroblastoma in Chinese population. *PLoS One*, 2013; 8: e71656
11. Wang J, Gao J, Li Y et al: Functional polymorphisms in FAS and FASL contribute to risk of squamous cell carcinoma of the larynx and hypopharynx in a Chinese population. *Gene*, 2013; 524: 193–96
12. Tong N, Zhang L, Sheng X et al: Functional polymorphisms in FAS, FASL and CASP8 genes and risk of childhood acute lymphoblastic leukemia: a case-control study. *Leuk Lymphoma*, 2012; 53: 1360–66
13. Shao P, Ding Q, Qin C et al: Functional polymorphisms in cell death pathway genes FAS and FAS ligand and risk of prostate cancer in a Chinese population. *Prostate*, 2011; 71: 1122–30
14. Zhu J, Qin C, Wang M et al: Functional polymorphisms in cell death pathway genes and risk of renal cell carcinoma. *Mol Carcinog*, 2010; 49: 810–17
15. Zhou RM, Wang N, Chen ZF et al: Polymorphisms in promoter region of FAS and FASL gene and risk of cardia gastric adenocarcinoma. *J Gastroenterol Hepatol*, 2010; 25: 555–61
16. Wang M, Wu D, Tan M et al: FAS and FAS ligand polymorphisms in the promoter regions and risk of gastric cancer in Southern China. *Biochem Genet*, 2009; 47: 559–68
17. Yang M, Sun T, Wang L et al: Functional variants in cell death pathway genes and risk of pancreatic cancer. *Clin Cancer Res*, 2008; 14: 3230–36
18. Hsu PI, Lu PJ, Wang EM et al: Polymorphisms of death pathway genes FAS and FASL and risk of premalignant gastric lesions. *Anticancer Res*, 2008; 28: 97–103
19. Kang S, Dong SM, Seo SS et al: FAS -1377 G/A polymorphism and the risk of lymph node metastasis in cervical cancer. *Cancer Genet Cytogenet*, 2008; 180: 1–5
20. Jung YJ, Kim YJ, Kim LH et al: Putative association of Fas and FasL gene polymorphisms with clinical outcomes of hepatitis B virus infection. *Intervirology*, 2007; 50: 369–76
21. Zhang B, Sun T, Xue L et al: Functional polymorphisms in FAS and FASL contribute to increased apoptosis of tumor infiltration lymphocytes and risk of breast cancer. *Carcinogenesis*, 2007; 28: 1067–73
22. Park SH, Choi JE, Kim EJ et al: Polymorphisms in the FAS and FASL genes and risk of lung cancer in a Korean population. *Lung Cancer*, 2006; 54: 303–8
23. Ikehara SK, Ikehara Y, Matsuo K et al: A polymorphism of C-to-T substitution at -31 IL1B is associated with the risk of advanced gastric adenocarcinoma in a Japanese population. *J Hum Genet*, 2006; 51: 927–33
24. Li C, Wu W, Liu J et al: Functional polymorphisms in the promoter regions of the FAS and FAS ligand genes and risk of bladder cancer in south China: a case-control analysis. *Pharmacogenet Genomics*, 2006; 16: 245–51
25. Sun T, Zhou Y, Li H et al: FASL -844C polymorphism is associated with increased activation-induced T cell death and risk of cervical cancer. *J Exp Med*, 2005; 202: 967–74
26. Sun T, Miao X, Zhang X et al: Polymorphisms of death pathway genes FAS and FASL in esophageal squamous-cell carcinoma. *J Natl Cancer Inst*, 2004; 96: 1030–36
27. Lai HC, Sytwu HK, Sun CA et al: Single nucleotide polymorphism at Fas promoter is associated with cervical carcinogenesis. *Int J Cancer*, 2003; 103: 221–25
28. Valibeigi B, Amirghofran Z, Golmoghaddam H et al: Fas Gene Variants in Childhood Acute Lymphoblastic Leukemia and Association with Prognosis. *Pathol Oncol Res*, 2013 [Epub ahead of print]
29. Kim SS, Hong SJ, Ahn YG et al: Apo-1/Fas(CD95) gene polymorphism in lorean hepatocellular carcinoma patients. *Korean J Physiol Pharmacol*, 2003; 7: 29–31
30. Chang L, Xiao MH, Yang H et al: Association between polymorphisms of FAS gene and FAS ligand in cell death pathway with risk of bladder cancer. *Chin J Exp Surg*, 2013; 30: 563–66
31. Lai HC, Lin WY, Lin YW et al: Genetic polymorphisms of FAS and FASL (CD95/CD95L) genes in cervical carcinogenesis: An analysis of haplotype and gene-gene interaction. *Gynecol Oncol*, 2005; 99: 113–18
32. Li Y, Hao YL, Kang S et al: Genetic polymorphisms in the Fas and FasL genes are associated with epithelial ovarian cancer risk and clinical outcomes. *Gynecol Oncol*, 2013; 128: 584–89
33. Ueda M, Terai Y, Kanda K et al: Fas gene promoter -670 polymorphism in gynecological cancer. *Int J Gynecol Cancer*, 2006; 16: 179–82
34. Jain M, Kumar S, Lal P et al: Role of BCL2 (ala43thr), CCND1 (G870A) and FAS (A-670G) polymorphisms in modulating the risk of developing esophageal cancer. *Cancer Detect Prev*, 2007; 31: 225–32
35. Zhu Q, Wang T, Ren J et al: FAS-670A/G polymorphism: A biomarker for the metastasis of nasopharyngeal carcinoma in a Chinese population. *Clin Chim Acta*, 2010; 411: 179–83
36. Gangwar R, Mittal RD: Association of selected variants in genes involved in cell cycle and apoptosis with bladder cancer risk in North Indian population. *DNA Cell Biol*, 2010; 29: 349–56
37. Kim HJ, Jin XM, Kim HN et al: Fas and FasL polymorphisms are not associated with acute myeloid leukemia risk in Koreans. *DNA Cell Biol*, 2010; 29: 619–24
38. Mandal RK, Mittal RD: Are cell cycle and apoptosis genes associated with prostate cancer risk in North Indian population? *Urol Oncol*, 2012; 30: 555–61
39. Hashemi M, Fazaeli A, Ghavami S et al: Functional polymorphisms of FAS and FASL gene and risk of breast cancer – pilot study of 134 cases. *PLoS One*, 2013; 8: e53075
40. Hu Y, Jin LY, Huang X, GEN PL: Association between Fas -670 gene polymorphism and gastric cancer risk in Qinghai region in China. *Shang Dong Yi Yao*, 2011; 51: 45–46
41. Li H, Guo HY, Sun T et al: Association between Fas/FasL gene promoter polymorphisms and pathogenic risk of cervical cancer. *Chin J Oncol*, 2009; 31: 38–41
42. Zhang J, Liu Q, Mao HT: Analyzing of Fas-670 gene polymorphism in hepatocarcinoma tissue. *Chin J Hepatol*, 2009; 17: 630–31
43. Chen XB, Chen GL, Liu JN et al: Genetic polymorphisms in STK15 and MMP-2 associated susceptibility to esophageal cancer in Mongolian population. *Chin J Prev Med*, 2009; 43: 559–63
44. Jemal A, Bray F, Center MM et al: Global cancer statistics. *CA Cancer J Clin*, 2011; 61: 69–90
45. Zaridze DG: Molecular epidemiology of cancer. *Biochemistry (Mosc)*, 2008; 73: 532–42
46. Lu J, Xu L, Zou Y et al: IDH1 p.R132 mutations may not be actively involved in the carcinogenesis of hepatocellular carcinoma. *Med Sci Monit*, 2015; 21: 247–54
47. Taura N, Ichikawa T, Miyaaki H et al: Frequency of elevated biomarkers in patients with cryptogenic hepatocellular carcinoma. *Med Sci Monit*, 2013; 19: 742–50
48. Suda T, Takahashi T, Golstein P, Nagata S: Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. *Cell*, 1993; 75: 1169–78
49. Pharoah PD, Dunning AM, Ponder BA, Easton DF et al: Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer*, 2004; 4: 850–60