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FASLG polymorphism is associated with cancer risk

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ABSTRACT

Many studies have reported the association between the *FASLG* –844T/C polymorphism and cancer risk, but the data are remaining controversial. A pooled analysis was performed to assess this relationship comprehensively. Medline, PubMed, Embase and Web of Science were searched, and data were extracted and cross-checked independently by three authors. A total of 18 published studies including 22389 subjects were involved in this analysis. Overall, the –844C allele was associated with a significantly increased cancer risk (for CC versus TT: OR = 1.23, 95% confidence interval (CI) = 1.04–1.45; for CC + TC versus TT: OR = 1.15, 95% CI = 1.01–1.30; for CC versus TT + TC: OR = 1.20, 95% CI = 1.05–1.38). In the subgroup analysis by ethnicity, significantly elevated risks were found among Asians (for CC versus TT: OR = 1.61, 95% CI = 1.37–1.89; for CC + TC versus TT: OR = 1.36, 95% CI = 1.16–1.60; for CC versus TT + TC: OR = 1.44, 95% CI = 1.22–1.70). In the subgroup analysis by study design, significantly increased risks were found among population-based case-control studies (for CC versus TT: OR = 1.40, 95% CI = 1.06–1.84; for CC + TC versus TT: OR = 1.25, 95% CI = 1.01–1.55; for CC versus TT + TC: OR = 1.31, 95% CI = 1.06–1.61). These findings indicate that the *FASLG* –844C allele is emerging as a low-penetrant cancer susceptibility allele for cancer development. However, more comprehensive understanding of the association would certainly have an immense prospect in the promising field of individualised preventive care.

1. Introduction

Recently, the 2008 edition of the World Cancer Report from the International Agency for Research on Cancer has reported that cancer will become the leading cause of death worldwide in the year 2010. Also, cancer has become a major public health challenge in Europe with about 3% prevalence, increasing to 15% among aged people. About 50% of deaths at middle age were caused by cancer. In 2002, almost 26% of all cancer cases in the world were diagnosed in Europe.[1,2] Although cancer prevention and management are moving towards the right direction, cancer prevention efforts still have much to do.[3] Potent markers for screening high-risk populations are urgently needed for early detection and preventive care. Genetic susceptibility genes combining with environmental factors have been suggested to play an important role in the cancer development.[4] Low-penetrant susceptibility markers are becoming an important guidance for early preventive

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care. Several common low-penetrant genes have been identified as potential cancer susceptibility markers. An important one is *FAS ligand* (*FASLG*), which plays an important role in the apoptosis and cancer development.[5] A functional single nucleotide polymorphism in promotor region at the –844th nucleotide (rs763110), with a T to C change,[6] has been reported by several studies to have an impact on cancer risk,[7–24] but the results are inconsistent. No quantitative summary of the evidence has ever been taken. Therefore, a pooled analysis was performed to get a better understanding of the association between this polymorphism and cancer risk.

2. Materials and methods

2.1. Literature identification

All studies reported the association of the *FASLG* –844T/C polymorphism and cancer risk and published before 10th September 2008 were identified by comprehensive searches of Medline, PubMed, Embase and Web of Science. The following terms were used for searching studies: '*FASL*', '*FASLG*', '*FAS ligand*', 'CD95L', 'polymorphism', 'variation' and 'cancer'. Titles and abstracts even full text of the retrieved studies were reviewed for determining whether the studies met the inclusion criteria. The references of all eligible studies and review articles were checked for other relevant publications. Duplicated articles were excluded. Only English and Chinese language articles were included.

2.2. Inclusion criteria

Studies evaluating the association between *FASLG* –844T/C polymorphism and cancer risk should meet the following criteria: (a) case-control studies; (b) the number of individual genotypes (TT, TC and CC) in cases and controls were supplied and (c) the total number of cases and controls was more than 100.

2.3. Data extraction

Data were extracted and cross-checked independently by three authors, and disagreement was discussed to arrive to consensus. Following information was collected for each study: first author's family name, publication date, ethnicity, cancer type, study design, the total number of participants in case and control groups, and the numbers of cases and controls with the every genotype, respectively. For information not found from full text, corresponding authors were contacted for the required data. Ethnicities were categorised as Caucasian and Asian, but no African study was found in these studies.

2.4. Statistical methods

All the statistical analyses were done by Stata version 10.0 (Stata Corporation, College Station, TX). Hardy–Weinberg equilibrium (HWE) in the controls was tested by the chi-square test for goodness of fit, and a $P < 0.05$ was considered as significant disequilibrium. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the association between *FASLG* –844T/C polymorphism and cancer risk. TC versus TT and CC versus TT (co-dominant model), CC + TC versus TT (dominant model) and CC versus TC + TT (recessive model) were estimated, respectively. Subgroup analyses by ethnicity, study design and cancer type were performed subsequently. Heterogeneity assumption was checked by the chi-square-based Q-test.[25] A $P < 0.10$ indicates a heterogeneity existing among the studies, so the random-effects model (the DerSimonian and Laird method) was used.[26] Otherwise, the fixed-effects model (the Mantel–Haenszel method) was used.[27] Sensitivity analysis was performed by deleting the studies not in HWE. Publication bias was assessed using Begg's funnel plots and Egger's linear regression test. An asymmetric plot suggests that a publication bias may exist, and the *P*-value of Egger's linear regression test less than 0.05 was considered as statistically significant publication bias.[28]

3. Results

3.1. Main characteristics

Table 1 lists the main information of all the involved studies. A total of 18 studies including 11,058 cases and 11,331 controls were eligible for pooling analysis.[7–24] There were ten studies of Asians and eight studies of Caucasians. Controls were mainly matched for sex and age. Nine were population-based case-control studies and nine were hospital-based. Only genotype distributions in the controls of the study of Sun and colleague deviated from HWE.[10]

3.2. Synthesis results

Main results of this meta-analysis are shown in Table 2. Overall, the –844C allele was associated with a significantly increased cancer risk when the 18 studies were pooled into the meta-analysis (for CC versus TT: OR = 1.23, 95% confidence interval (CI) = 1.04–1.45; for dominant model: OR = 1.15, 95% CI = 1.01–1.30; for recessive model: OR = 1.20, 95% CI = 1.05–1.38). In the subgroup analysis by ethnicity, significantly elevated risks were found among Asians (for CC versus TT: OR = 1.61, 95% CI = 1.37–1.89; for CC + TC versus TT: OR = 1.36, 95% CI = 1.16–1.60; for CC versus TT + TC: OR = 1.44, 95% CI = 1.22–1.70). However, no obvious associations were observed in Caucasians. In the subgroup analysis by study design, obviously increased risks were observed among population-based case-control studies (for CC versus TT: OR = 1.40, 95% CI = 1.06–1.84; for CC + TC versus TT: OR = 1.25, 95% CI = 1.01–1.55; for CC versus TT + TC: OR = 1.31, 95% CI = 1.06–1.61), but no obvious associations were found among studies with hospital-based controls. Sensitivity analysis by deleting the study of Sun and colleague which is not in HWE did not change all the results significantly.

3.3. Publication bias test

No evidence of obvious asymmetry were found from the shapes of the funnel plots in all comparison models (figures not shown). The results of the Egger's test also showed no

Table 1 – Main characteristics of all involved studies.

Surname	Year	Ethnicity	Cancer type	Study design	Case/control	C% (case)	C% (control)	HWE
Ter-Minassi	2008	Caucasian	Lung	Hospital	2174/1497	61	62	Y
Hsu	2008	Asian	Gastric	Hospital	86/101	73	64	Y
Kang	2008	Asian	Cervical	Hospital	154/160	77	69	Y
Yang	2008	Asian	Pancreatic	Population	397/907	78	71	Y
Ivansson	2007	Caucasian	Cervical	Population	1284/280	70	71	Y
Zhang	2007	Caucasian	Melanoma	Population	229/351	70	75	Y
Zhang	2007	Asian	Breast	Population	839/830	76	72	Y
Crew	2007	Caucasian	Breast	Population	1062/1105	57	57	Y
Erdogan	2007	Caucasian	Thyroid	Hospital	45/100	63	67	Y
Li	2006	Asian	Bladder	Hospital	216/252	70	75	Y
Park	2006	Asian	Lung	Hospital	582/582	72	72	Y
Li	2006	Caucasian	Melanoma	Hospital	602/603	71	72	Y
Zhang	2006	Caucasian	SCCHN	Hospital	721/1234	67	65	Y
Lai	2005	Asian	Cervical	Hospital	303/316	73	71	Y
Sun	2005	Asian	Cervical	Population	314/615	79	70	N
Zhang	2005	Asian	Lung	Population	1000/1270	77	69	Y
Sun	2004	Asian	Esophageal	Population	588/648	77	68	Y
Krippl	2004	Caucasian	Breast	Population	489/487	66	64	Y

SCCHN, squamous cell carcinoma of the head and neck; C% (case), C allele frequency in cases; C% (control), C allele frequency in controls; HWE, Hardy–Weinberg equilibrium.

Table 2 – Main results of the FASLG –844T/C polymorphism and cancer risk.

	N	TC versus TT OR(95%CI) P_h	CC versus TT OR(95%CI) P_h	CC + TC versus TT OR(95%CI) P_h	CC versus TT + TC OR(95%CI) P_h
Total	18	1.07(0.97–1.17) 0.29	1.23(1.04–1.45) 0.00	1.15(1.01–1.30) 0.06	1.20(1.05–1.38) 0.00
Ethnicity					
Asian	10	1.09(0.92–1.28) 0.31	1.61(1.37–1.89) 0.10	1.36(1.16–1.60) 0.29	1.44(1.22–1.70) 0.00
Caucasian	8	1.06(0.95–1.19) 0.23	1.01(0.90–1.14) 0.26	1.04(0.93–1.16) 0.21	0.97(0.90–1.05) 0.75
Control source					
Hospital	9	1.06(0.92–1.21) 0.14	1.05(0.91–1.20) 0.66	1.05(0.93–1.20) 0.66	1.02(0.94–1.11) 0.17
Population	9	1.08(0.95–1.23) 0.49	1.40(1.06–1.84) 0.00	1.25(1.01–1.55) 0.01	1.31(1.06–1.61) 0.00
Cancer types					
Breast	3	1.13(0.94–1.35) 0.42	1.17(0.97–1.41) 0.01	1.15(0.97–1.36) 0.26	1.11(0.91–1.36) 0.06
Cervical	4	0.84(0.63–1.12) 0.15	0.98(0.66–1.45) 0.20	0.88(0.67–1.14) 0.17	1.10(0.77–1.56) 0.22
Lung	3	1.05(0.90–1.23) 0.88	1.19(0.81–1.74) 0.01	1.10(0.95–1.27) 0.29	1.17(0.77–1.80) 0.00

P_h: *P*-value of heterogeneity test.

evidence of publication bias (*P* = 0.50 for TC versus TT; *P* = 0.44 for CC versus TT; *P* = 0.72 for dominant model and *P* = 0.70 for recessive model).

4. Discussion

A systematic review approach may assist in estimating the population-wide effects of a genetic risk factor in human disease and may provide a quantitative approach for combining the data of various studies on the same topic and for explaining their diversity. Recently, a meta-analysis indicated that the *FAS* –1377G/A polymorphism was associated with cancer risk.[29] Because of the important role of FAS–FASLG-mediated death pathway in the life and carcinogenesis and the close relation of FAS and FASLG, we conducted a meta-analysis to estimate the association between *FASLG* –844T/C polymorphism and cancer risk. To our knowledge, this was the first meta-analysis concerning this polymorphism and cancer susceptibility, which included 18 studies involving 11,058 cases and 11,331 controls.

Our results indicated that the –844C allele was associated with a significantly increased cancer risk when the 18 studies were pooled into the meta-analysis. This finding may be biologically plausible. It has been proven that *FASLG* –844T/C polymorphism has a substantial impact on promotor activity of the *FASLG* genes by an *in vitro* assay because of its location in a binding motif for transcription factor CAAT/enhancer-binding protein.[6] Additionally, this variation strongly affected the FASLG expression ex vivo on T cells.[10] It was demonstrated that the *FASLG* –844C allele, with higher expression of FASLG on T cells, could enhance the rate of AICD of T cells.[10] Because of the important role played by

the FASLG–FAS-mediated AICD in the tumour-infiltration lymphocyte (TIL) apoptosis occurring in the tumour microenvironment, the *FASLG* –844C allele carriers, who have higher FASLG expression on T cells on tumour antigenic stimulation, would be anticipated to be at risk of developing cancer.[30] Elevated FASLG expression may stimulate the transformed cells to counterattack the FAS expressing TILs, leading to immune evasion of these malignant cells.[31] All these suggested that subjects carrying the C allele have an increased cancer risk.

The results of subgroup analysis based on ethnicity indicated that the association between the *FASLG* –844T/C polymorphism and the cancer risk was obvious among Asians but not among Caucasians. The reason for Asians having a higher risk of cancer might be a higher frequency of C allele among them. The frequency of –844C allele among Asians was much higher than that among Caucasians (71% versus 64%), which suggested that this variant allele might be distributed differently between the two ethnicities. Another possible explanation for the ethnic discrepancy is that *FASLG* –844T/C polymorphism may be in linkage disequilibrium with the true causal polymorphism that is in a higher frequency in Asians. Additionally, the different genetic backgrounds and different environments the two ethnicities lived in might also contribute to the ethnic discrepancy.

Our results indicated that significantly increased risks of *FASLG* –844C alleles were found among studies using the population-based controls but not among those using hospital-based controls. This may be due to that the hospital-based case-control studies have some selection biases because such controls might be ill-related population, and may not be a representative of the general population, especially when the investigated genotypes were associated with the disease conditions hospital-based controls might have. Although hospital controls are relatively easier, more convenient and economical to be recruited, a proper population-based control subject is much better to reduce biases in such genetic association studies.

Overall, there existed some significant between-study heterogeneity when the 18 studies were pooled into the meta-analysis. However, the heterogeneity was effectively decreased when subgroup analysis by ethnicity or by cancer type was performed. The explanation might be that different genetic backgrounds and different environments may exist among different ethnicities, and different mechanisms of carcinogenesis may exist among different kinds of cancer.

In conclusion, this meta-analysis suggests that the *FASLG* –844T/C polymorphism is associated with cancer risk and the –844C allele is a low-penetrant risk factor for cancer development. However, many exhaustive studies involving a large sample size of the same kind of cancer patients, well-matched controls, and considering the variables such as polymorphisms in linkage disequilibrium, gene-gene and gene-environment interactions are required to acquire a total knowledge on the association between the *FASLG* –844T/C polymorphism and the cancer risk. This comprehensive understanding of the association would certainly have an immense prospect in the promising field of individualised preventive care.

Conflict of interest statement

None declared.

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