Association of Fas -1377 G/A Polymorphism with Susceptibility to Cancer

Peiliang Geng*, Jianjun Li*, Juanjuan Ou, Ganfeng Xie, Ning Wang, Lisha Xiang, Rina Sa, Chen Liu, Hongtao Li, Houjie Liang*
Department of Oncology and Southwest Cancer Center, Southwest Hospital, Third Military Medical University, Chongqing, P.R. China

Abstract

**Background:** The relationship between Fas -1377 G/A polymorphism and cancer susceptibility has been implicated in accumulating data. However, the data presented inconsistent results. This study was devised to investigate the association of Fas -1377 G/A polymorphism and cancer susceptibility in a large number of participants.

**Methods:** The databases of PubMed, Embase, and Web of Science were searched and a total of 27 case-control studies including 13,355 cases and 16,078 controls were included in this meta-analysis. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the fixed-effects model. Statistical analyses were performed by using Stata software.

**Results:** The results suggested that Fas -1377 G/A polymorphism was overall associated with cancer susceptibility (additive model: OR, 1.16, 95%CI = 1.06–1.27, $P_{\text{heterogeneity}} = 0.381$; recessive model: OR, 1.19, 95%CI = 1.10–1.29, $P_{\text{heterogeneity}} = 0.137$). In the subgroup analysis by cancer type, significantly increased risk was observed in breast cancer (additive model: OR, 1.24, 95%CI = 1.04–1.58, $P_{\text{heterogeneity}} = 0.614$; recessive model: OR, 1.24, 95%CI = 1.02–1.51, $P_{\text{heterogeneity}} = 0.349$) and lung cancer (recessive model: OR, 1.25, 95%CI = 1.04–1.49, $P_{\text{heterogeneity}} = 0.090$). Similarly, elevated cancer risk associated with Fas -1377 G/A polymorphism was revealed in Asians.

**Conclusions:** The combined results suggest that Fas -1377 G/A polymorphism might modulate cancer susceptibility in an Asian-specific manner.

Introduction

Cancer arises as a result of complex interactions between genetic and environmental factors and has become a major public health problem all over the world [1–5]. In recent years, many individual studies have set out to determine whether there is an association between genetic polymorphisms and cancer susceptibility, such as Fas -1377 G/A polymorphism and cancer susceptibility. However, these studies showed conflicting results that failed to provide compelling evidence for cancer susceptibility [6–9].

Apoptosis is a process of programmed cell death regulated by genes. Inappropriate regulation of apoptosis could lead to a broad range of human disorders including cancer [10–13]. Fas is a member of the tumor necrosis factor receptor superfamily and regulates apoptotic activities in activated lymphocytes [14]. Located on chromosome 10q24.1, Fas is highly polymorphic [15]. A functional polymorphism with a G to A substitution at -1377 position within the Fas gene has been extensively explored in the field of cancer. But there is no decisive conclusion of the role of this polymorphism in cancer development [6,7]. In addition, several studies have been subsequently published since a previous meta-analysis was reported in 2009 [47]. In view of this, we decided to carry out a meta-analysis including 27 eligible studies published to date to systematically and comprehensively estimate the association between Fas -1377 G/A polymorphism and susceptibility to cancer.

Materials and Methods

**Literature Search Strategy**

The databases of PubMed, Embase, and Web of Science were searched (the last search was updated in May 2013) to identify all relevant publications on the association between Fas -1377 G/A polymorphism and cancer risk. The following search terms and their synonyms were used: “Fas”, “1377 G/A” or “CD95” or “rs2234767”, “polymorphism” or “variation”, and “cancer”. We also manually searched the reference lists of all eligible studies and review articles to obtain additional usable data that can be included in the current meta-analysis.
Inclusion Criteria and Exclusion Criteria

We selected eligible studies according to the following criteria: (1) the study must have a case-control design; (2) the association between Fas -1377 G/A polymorphisms and cancer risk must be examined; (3) adequate genotyping data must be contained such that odds ratios (ORs) with 95% confidence intervals (CIs) could be calculated; (4) the study had to be published in English and use human subjects. Exclusion criteria were: (1) insufficient information on the distribution of Fas -1377 genotypes; (2) case-only studies; (3) duplicated publications. If a study was subsequently updated, we selected the study with the largest sample size. Two investigators independently reviewed all studies to examine whether they fulfilled the inclusion criteria.

Data Extraction

Two independent investigators (Peiliang Geng and Jianjun Li) extracted the original data according to the inclusion criteria and exclusion criteria to ensure the accuracy of the retrieved information. The data extracted from each eligible study included the first author’s name, year of publication, cancer type, ethnicity, source of controls, method adopted for genotyping, number of cases and controls and genotype frequencies. Disputes were settled by consulting the third person (Houjie Liang).

Statistical Analysis

Crude ORs with 95% CIs were calculated to evaluate the strength of the association between Fas -1377 G/A polymorphism and cancer risk. The pooled ORs were performed for additive model, dominant model and recessive model. Subgroup analysis by cancer type, ethnicity and source of control were also conducted to further assess if the Fas -1377 polymorphism was associated with cancer susceptibility in each subgroup. Heterogeneity assumption was evaluated by the chi-square based Q-test and I² statistics [16,17]. P>0.05 for the Q test or I²<50% suggested a lack of heterogeneity. In this situation, the OR of each study was calculated by the fixed-effects model (the Mantel-Haenszel method) [10]. If P<0.05 or I²>50%, the random-effects model (the DerSimonian and Laird method) was used [19]. Sensitivity analysis was performed by removing one study at a time to ensure that our findings were not driven by any single study. The evaluation of potential publication bias was performed using the Begg’s funnel plots and Egger’s test [20]. Hardy-Weinberg equilibrium (HWE) of the control groups was tested by the χ² test for goodness of fit. All statistical analyses were performed by STATA version 12.0 (Stata Corporation, College Station, TX, USA). A level of P<0.05 was accepted as statistically significant.

Results

Study Characteristics

We initially identified 147 potentially relevant studies, of which 27 met the pre-described inclusion criteria and were included in the meta-analysis of the association between Fas -1377G/A polymorphism and cancer risk (Figure 1). Characteristics of all eligible case-control studies for the relationship of Fas -1377G/A polymorphism with cancer risk are summarized in Table 1. The subgroup analysis was carried out by cancer type, ethnicity and source of control, respectively. Genotype frequencies were available in all of the 27 studies.

Meta-analysis

Major results of the meta-analysis are presented in Table 2. No significant between-study heterogeneity was detected across studies and thus we selected the fix-effects model to summarize the ORs. Overall, we found a significant association between Fas -1377G/A polymorphism and cancer risk under the additive model (OR, 1.16, 95%CI = 1.06–1.27, PHeterogeneity = 0.381), but the association was more pronounced under the recessive model (OR, 1.19, 95%CI = 1.10–1.29, PHeterogeneity = 0.137) (Figure 2, 3). In the subgroup analysis by cancer type, significantly increased risk was observed in breast cancer (additive model: OR, 1.24,
| Authors Year | Source of control | Ethnicity | Cancer type | Genotyping method | Case Sample size | GG | GA | AA | G | A | Control Sample size | GG | GA | AA | G | A | HWE |
|--------------|------------------|----------|-------------|-------------------|-----------------|----|----|----|----|----|--------------------|----|----|----|----|----|------|
| Sibley 2003  | Population       | European | AML         | PCR–RFLP          | 471             | 319| 136| 16  | 774| 16  | 931               | 726| 186| 19  | 1638| 224| 0.087 |
| Sun 2004     | Population       | Asian    | Esophageal  | PCR–RFLP          | 588             | 250| 234| 104 | 734| 442 | 648               | 273| 306| 69  | 852 | 444| 0.218 |
| Kipple 2004  | Population       | European | Breast      | TaqMan            | 499             | 371| 120| 8   | 862| 136 | 497               | 401| 92  | 4   | 894 | 100| 0.610 |
| Li 2005      | Hospital         | Asian    | Cervical    | TaqMan            | 318             | 127| 138| 53  | 392| 244 | 318               | 99  | 165| 54  | 3633| 273| 0.293 |
| Sun 2005     | Population       | Asian    | Cervical    | PCR–RFLP          | 314             | 144| 144| 26  | 432| 196 | 615               | 282| 277| 56  | 841 | 389| 0.304 |
| Zhang 2005   | Population       | Asian    | Lung        | PCR–RFLP          | 1000            | 413| 433| 154 | 1259| 741 | 1270              | 539| 601| 130 | 1679| 861| 0.046 |
| Li 2006      | Hospital         | Asian    | Bladder     | PCR–RFLP          | 216             | 66 | 104| 46  | 236| 196 | 252               | 81  | 124| 47  | 286 | 218| 0.970 |
| Park 2006    | Hospital         | Asian    | Lung        | PCR–RFLP          | 582             | 187| 300| 95  | 674| 490 | 582               | 172| 313| 97  | 657 | 507| 0.024 |
| Li 2006      | Hospital         | European | Melanoma    | PCR–RFLP          | 602             | 486| 107| 9   | 1079| 125| 603               | 459| 134| 10  | 1052| 154| 0.951 |
| Zhang 2006   | Hospital         | European | SCCHN       | PCR–RFLP          | 721             | 562| 142| 17  | 1266| 176| 1234              | 957| 264| 13  | 2178| 290| 0.268 |
| Gormas 2007  | Population       | European | Lung        | PCR               | 94              | 21 | 73 | 0   | 115 | 73  | 50                | 13 | 37  | 0   | 63  | 37 | >0.05 |
| Zhang 2007   | Population       | Asian    | Breast      | PCR–RFLP          | 840             | 293| 418| 129 | 1004| 676 | 839               | 345| 382| 112 | 1072| 606| 0.700 |
| Crew 2007    | Population       | European | Breast      | TaqMan            | 1057            | 809| 225| 23  | 1843| 271 | 1106              | 847| 234| 25  | 1928| 284| 0.069 |
| Koshkina 2007| Hospital         | European | Osteosarcoma| PCR–RFLP          | 123             | 99 | 22 | 2   | 220| 26  | 510               | 400| 100| 10  | 900  |120 | 0.210 |
| Zhang 2007   | Population       | European | Melanoma    | PCR–RFLP          | 229             | 183| 41 | 5   | 407 | 51  | 351               | 269| 70 | 12  | 608  | 94 | 0.009 |
| Ter-Minassi 2008| Hospital       | European | Lung        | TaqMan            | 2174            | 1645| 492| 37  | 3782| 566 | 1497              | 1138| 336| 23  | 2612| 382| 0.751 |
| Kang 2008    | Population       | Asian    | Cervical    | PCR–RFLP          | 154             | 54 | 69 | 31  | 177 | 131 | 168               | 56 | 82 | 20  | 194  | 142| 0.998 |
| Yang 2008    | Population       | Asian    | Pancreatic  | PCR–RFLP          | 397             | 186| 169| 42  | 541 | 253 | 907               | 420| 376| 111 | 1216 | 598| 0.062 |
| Zhou 2009    | Population       | Asian    | Gastric     | PCR–RFLP          | 262             | 124| 117| 21  | 365 | 159 | 524               | 225| 251| 48  | 701  | 347| 0.062 |
| Cao 2010     | Population       | Asian    | Nasopharyngeal | PCR–RFLP         | 576             | 141| 264| 171 | 546| 606 | 608               | 172| 303| 133 | 647  | 569| 0.984 |
| Kim 2010     | Population       | Asian    | AML         | PCR               | 592             | 195| 303| 94  | 693 | 491 | 858               | 286| 427| 145 | 999  | 717| 0.501 |
| Wang 2010    | Population       | Asian    | Oral        | PCR–RFLP          | 431             | 146| 208| 77  | 500 | 362 | 333               | 115| 165| 53  | 395  | 271| 0.628 |
| Zhu 2010     | Hospital         | Asian    | Renal       | PCR–RFLP          | 353             | 124| 173| 56  | 421 | 285 | 365               | 161| 161| 43  | 483  | 247| 0.777 |
| Kupcinskas 2011| Hospital       | European | Gastric     | TaqMan            | 114             | 95 | 18 | 1   | 208 | 20  | 238               | 197| 40 | 1   | 434  | 42 | 0.492 |
| Wang 2012    | Hospital         | Asian    | Breast      | PCR–RFLP          | 375             | 138| 171| 66  | 447 | 303 | 496               | 197| 246| 53  | 640  | 352| 0.064 |
| Hashemi 2013 | Population       | Asian    | Breast      | PCR               | 134             | 20 | 106| 8   | 146 | 122 | 152               | 26 | 115| 11  | 167  | 137| >0.05 |
| Karimi 2013  | Population       | Asian    | Oral        | PCR–RFLP          | 139             | 88 | 42 | 9   | 218 | 60  | 126               | 84 | 30 | 12  | 198  | 54 | 0.001 |

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; TaqMan: TaqManSNP; AML: acute myeloid leukemia; SCCHN: squamous cell carcinoma of the head and neck; HWE: Hardy-Weinberg equilibrium.

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Table 2. Main results of the pooled data in the meta-analysis.

| Subtypes     | Additive model | Dominant model | Recessive model |
|--------------|----------------|----------------|-----------------|
|              | OR (95% CI)    | Heterogeneity  | OR (95% CI)     | Heterogeneity  | OR (95% CI)     | Heterogeneity  |
|              | P_h I^2 (%)    |                | P_h I^2 (%)     |                | P_h I^2 (%)     |                |
| Cancer type  |                |                |                 |                |                 |                |
| AML          | 1.07 (0.82, 1.14) | 0.080 67.4 | 1.14 (0.99, 1.30) | 0.011 84.6 | 1.02 (0.79, 1.32) | 0.125 57.6 |
| Breast       | 1.28 (1.04, 1.58) | 0.614 0 | 1.08 (0.99, 1.19) | 0.602 0 | 1.24 (1.02, 1.51) | 0.349 10.0 |
| Cervical     | 0.96 (0.72, 1.29) | 0.432 0 | 0.96 (0.83, 1.12) | 0.590 0 | 1.08 (0.82, 1.42) | 0.245 28.9 |
| Lung         | 1.19 (0.98, 1.43) | 0.163 45.0 | 1.01 (0.92, 1.10) | 0.960 0 | 1.25 (1.04, 1.49) | 0.090 58.4 |
| Melanoma     | 0.74 (0.37, 1.47) | 0.659 0 | 0.82 (0.66, 1.03) | 0.795 0 | 0.77 (0.39, 1.53) | 0.627 0 |
| Gastric      | 0.85 (0.50, 1.46) | 0.526 0 | 0.93 (0.74, 1.17) | 0.885 0 | 0.90 (0.53, 1.52) | 0.547 0 |
| Oral         | 1.03 (0.71, 1.48) | 0.444 0 | 1.03 (0.84, 1.26) | 0.749 0 | 1.04 (0.74, 1.47) | 0.313 1.9 |
| Other        | 1.26 (1.08, 1.47) | 0.301 16.9 | 1.02 (0.94, 1.11) | 0.940 0 | 1.31 (1.13, 1.52) | 0.139 38.0 |
| Ethnicity    |                |                |                 |                |                 |                |
| European     | 1.23 (0.94, 1.60) | 0.419 1.8 | 1.04 (0.96, 1.13) | 0.069 43.4 | 1.22 (0.93, 1.58) | 0.519 0 |
| Asian        | 1.15 (1.05, 1.26) | 0.318 11.6 | 1.02 (0.97, 1.07) | 0.994 0 | 1.19 (1.09, 1.30) | 0.060 37.4 |
| Source of control |            |                |                 |                |                 |                |
| Population   | 1.16 (1.05, 1.29) | 0.383 6.1 | 1.05 (0.99, 1.10) | 0.587 0 | 1.19 (1.08, 1.32) | 0.073 36.4 |
| Hospital     | 1.15 (0.97, 1.35) | 0.311 14.3 | 0.99 (0.92, 1.06) | 0.783 0 | 1.19 (1.02, 1.39) | 0.419 2.2 |
| Total        | 1.16 (1.06, 1.27) | 0.381 5.7 | 1.02 (0.98, 1.07) | 0.722 0 | 1.19 (1.10, 1.29) | 0.137 23.7 |
| Total^       | 1.16 (1.05, 1.28) | 0.484 0 | 1.03 (0.98, 1.08) | 0.583 0 | 1.19 (1.08, 1.30) | 0.249 15.8 |

AML: acute myeloid leukemia; CI: confidence interval; OR: odds ratio; ^meta-analysis results after removing the studies deviating from Hardy-Weinberg equilibrium (HWE).  

The human \textit{Fas} gene mapped on chromosome 10q24.1 consists of nine exons and eight introns [15]. -1377 G/A polymorphism, located in the promoter region of the \textit{Fas} gene, has been investigated in a variety of previous studies looking at cancer risk [8,21,22,26]. However, these findings remain controversial rather than conclusive. This might be attributed to the different ethnicities, distinct study design, and sample inadequacy in each of the published studies. But meta-analysis could avoid the shortcomings and convincingly estimate the genetic association through including all relevant studies.

In our meta-analysis, we observed \textit{Fas} -1377 G/A polymorphism was overall associated with cancer susceptibility under the additive model and the recessive model. Several published meta-analyses observed the same finding that \textit{Fas} -1377 G/A polymorphism was associated with cancer risk as well as some common diseases, such as autoimmune rheumatic diseases, systemic lupus erythematosus [44–47]. The detection power of the four meta-analyses, however, may be limited largely because of sample insufficiency: 4 publications (996 cases and 1,160 controls) were included by Lu et al. [44], 5 (615 cases and 622 controls) by Lee et al. [45], 5 (444 cases and 442 controls) by Xiang et al. [46] and 17 (10,564 cases and 12,075 controls) by Qiu et al. [47]. Our meta-analysis nevertheless summarized data from 27 studies composed of 13,355 cases and 12,075 controls. It should be noted that study size is obviously limited largely because of sample insufficiency: 4 publications (996 cases and 1,160 controls) were included by Lu et al. [44], 5 (615 cases and 622 controls) by Lee et al. [45], 5 (444 cases and 442 controls) by Xiang et al. [46] and 17 (10,564 cases and 12,075 controls) by Qiu et al. [47].
Apart from the comparison among all subjects, we also performed stratification analysis by cancer type. We found that Fas -1377 G/A polymorphism increased the risk of some cancers, such as breast cancer and lung cancer. Our findings were consistent with those revealed in the previous studies [6,9,21,26], but contradictory discoveries that there was no association between Fas -1377 G/A polymorphism and lung cancer were also suggested in two studies [7,8]. The underlying etiology mechanisms differ substantially across cancers, and the role of Fas -1377 G/A polymorphism in various cancers requires to be identified by future larger studies.

In addition, in the subgroup analysis by ethnicity, Fas -1377 G/A polymorphism was found to increase cancer risk in Asian populations under several genetic models, such as the recessive model and the additive model. However, this association was obtained in European populations. There is obvious disparity in genotype frequencies between the two ethnic groups (GA: 21.3% vs 47.7%; AA: 1.5% vs 13.2%). It is known that different genetic background donates a series of differences between ethnic groups, for instance, frequency of exposure to cancer-causing agents and diverse lifestyles, which are important components in the process of cancer progression.

In the final subgroup analysis by control source, we observed significant association in both population-based and hospital-based studies. However, investigators demonstrated a different discovery of significantly increased cancer risk associated with Fas -1377 AA genotype among studies based on population-based controls, but not among studies of hospital-based controls [47]. Control subjects in some hospital-based studies may be poorly-defined reference populations and failed to well represent the general population.
Figure 3. Meta-analysis for the association between Fas -1377 G/A polymorphism and cancer risk by fixed-effects model (recessive model; stratified by ethnicity).

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| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Sibley (2003) | 1.66 (0.85, 3.27) | 1.22 |
| Kriple (2004) | 1.99 (0.60, 6.66) | 0.39 |
| Li (2006) | 0.90 (0.36, 2.23) | 0.97 |
| Zhang (2006) | 2.24 (1.08, 4.63) | 0.93 |
| Crew (2007) | 0.96 (0.54, 1.71) | 2.35 |
| Koakhina (2007) | 0.83 (0.18, 3.83) | 0.37 |
| Zhang (2007) | 0.64 (0.22, 1.84) | 0.90 |
| Ter-Minassai (2008) | 1.11 (0.66, 1.87) | 2.63 |
| Kupcinskas (2011) | 2.09 (0.13, 33.68) | 0.06 |
| Subtotal (I-squared = 0.0%, p = 0.519) | 1.22 (0.93, 1.58) | 9.82 |

Asian

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Sun (2004) | 1.66 (1.20, 2.30) | 5.65 |
| Lai (2005) | 0.98 (0.65, 1.48) | 4.54 |
| Sun (2005) | 0.91 (0.56, 1.48) | 3.41 |
| Zhang (2005) | 1.50 (1.17, 1.93) | 9.99 |
| Li (2006) | 1.14 (0.73, 1.78) | 3.55 |
| Park (2006) | 0.98 (0.72, 1.33) | 8.17 |
| Zhang (2007) | 1.15 (0.88, 1.51) | 9.62 |
| Kang (2008) | 1.69 (0.93, 3.09) | 1.02 |
| Yang (2008) | 0.86 (0.59, 1.26) | 5.94 |
| Zhou (2009) | 0.88 (0.51, 1.49) | 2.89 |
| Cao (2010) | 1.36 (1.05, 1.75) | 10.11 |
| Kim (2010) | 0.94 (0.71, 1.24) | 9.98 |
| Wang (2010) | 1.12 (0.77, 1.64) | 5.02 |
| Zhu (2010) | 1.35 (0.88, 2.06) | 3.65 |
| Wang (2012) | 1.65 (1.12, 2.42) | 3.94 |
| Hashemi (2013) | 0.82 (0.32, 2.11) | 0.96 |
| Karimi (2013) | 0.68 (0.28, 1.67) | 1.15 |
| Subtotal (I-squared = 37.4%, p = 0.060) | 1.19 (1.09, 1.30) | 90.18 |
| Overall (I-squared = 23.7%, p = 0.137) | 1.19 (1.10, 1.29) | 100.00 |

Figure 4. Publication bias test for all included studies (additive model).

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leading to some biases in the analysis, but the relatively small sample may be responsible for a large part of the inconsistency.

Some limitations in our meta-analysis need to be addressed. To begin with, in the subgroup analysis by cancer type, significant other ethnicities. European populations, thus the results can not be applicable in Furthermore, there existed heterogeneity between studies. The which may be masked due to the small sample size in this study. Finally, this meta-analysis was carried out among Asian and European populations, thus the results can not be applicable in other ethnicities.

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In summary, the meta-analysis provided evidence that Fas -1377 G/A polymorphism might be associated with an increased cancer risk. Significant association was also found in subgroup analyses by cancer type, ethnicity and source of control. In future, studies with a larger sample size and multiple ethnic groups are required to further validate the relationship between Fas -1377 G/A polymorphism and cancer susceptibility.

Author Contributions

Conceived and designed the experiments: PG JL NW. Performed the experiments: JO GX LX. Analyzed the data: RS CL. Contributed reagents/materials/analysis tools: H. Li. Wrote the paper: H. Liang.
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