Association of the Polymorphisms in the *Fas/FasL* Promoter Regions with Cancer Susceptibility: A Systematic Review and Meta-Analysis of 52 Studies

Yeqiong Xu¹*, Bangshun He¹*, Rui Li²*, Yuqin Pan¹, Tianyi Gao¹, Qiwen Deng¹, Huiling Sun², Guoqi Song¹, Shukui Wang¹*

1 Central Laboratory, Nanjing First Hospital, Nanjing Medical University, Nanjing, China, 2 Department of Life Sciences, Nanjing Normal University, Nanjing, China

Abstract

Fas and its ligand (FasL) play an important role in apoptosis and carcinogenesis. Therefore, the potential association of polymorphisms in the *Fas* (-670A>G, rs1800682; -1377G>A, rs2234767) and *FasL* (-844C>T, rs763110) with cancer risk has been widely investigated. However, all the currently available results are not always consistent. In this work, we performed a meta-analysis to further determine whether carriers of the polymorphisms in *Fas* and *FasL* of interest could confer an altered susceptibility to cancer. All relevant data were retrieved by PubMed and Web of Science, and 52 eligible studies were chosen for this meta-analysis. There was no association of the *Fas* -670A>G polymorphism with cancer risk in the pooled data. For the *Fas* -1377G>A and *FasL* -844C>T polymorphisms, results revealed that the homozygotes of -1377A and -844C were associated with elevated risk of cancer as a whole. Further stratified analysis indicated markedly increased risk for developing breast cancer, gastric cancer, and esophageal cancer, in particular in Asian population. We conclude that carriers of the *Fas*-1377A and the *FasL* -844C are more susceptible to the majority of cancers than non-carriers.

Citation: Xu Y, He B, Li R, Pan Y, Gao T, et al. (2014) Association of the Polymorphisms in the *Fas*/FasL Promoter Regions with Cancer Susceptibility: A Systematic Review and Meta-Analysis of 52 Studies. PLOS ONE 9(3): e90090. doi:10.1371/journal.pone.0090090

Editor: Qing-Yi Wei, Duke Cancer Institute, United States of America

Received July 12, 2013; Accepted January 28, 2014; Published March 5, 2014

Copyright: © 2014 Xu et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work was supported by Program of Healthy Talents’ Cultivation for Nanjing City, and Social Development Technology Projects of Nanjing City, China (QYK11175). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: shukwang@163.com

† These authors contributed equally to this work.

Introduction

With new cases and mortality increased dramatically, cancer has become the major public health burden worldwide. For this reason, novel diagnostic markers are needed urgently for early detection and prevention of cancer. However, carcinogenesis is a complicated biological process that is not fully understood. It is generally believed that interactions of low-penetrance susceptibility genes with environmental factors might contribute to carcinogenesis [1]. As one of the important low-penetrance genes, *Fas* is considered to be a potential cancer susceptibility gene. This is because Fas (TNFSF6, CD95, or APO-1) is a cell surface receptor involved in apoptotic signal transmission in many cell types and interacts with its natural ligand Fas ligand (also known as FasL) to initiate the death signal cascade that leads to apoptotic cell death [2,3]. Furthermore, in these two genes, there are several functionally significant polymorphisms, such as the -670A>G and -1377G>A in the *Fas* promoter region, and the -844C>T in the *FasL* promoter region, because they might be associated with cancer risk, including cervical cancer [4–9], gastric cancer [10–15], breast cancer [16–21], lung cancer [22–25] and so on. However, all available results are not always consistent with one another, partially because of the small sample size of some published studies, different ethnic backgrounds, publication bias, and little effect of the polymorphisms on cancer risk. Therefore, it's necessary to retrieve and pool all eligible data to further determine whether these genetic polymorphisms could be at increased risk for developing cancer and to what extent heterogeneity existed across all the studies.

Materials and Methods

Identification and eligibility of relevant studies

Two online medical databases, PubMed, and Web of Science, were searched (updated February 2013), using the search terms “Fas/CD95/TNFSF6/APO-1”, “FasL/CD95L”, “polymorphism/genetic variation” and “cancer/carcinoma/tumor”). The literature search was limited to English articles. In addition, more studies were also identified by manual search based on the references provided in the retrieved studies. The inclusion criteria were prespecified as below: (1) be a case-control study, (2) evaluate association between the *Fas* and/or *FasL* polymorphisms and cancer risk, (3) present sufficient data to calculate an odds ratio (OR) with 95% confidence interval (CI), and (4) list genotype frequency. Moreover, the studies without raw data, or those that were case-only studies, case reports, editorials, and review articles (including meta-analyses) were eliminated.

Data extraction

Information was extracted carefully from all eligible articles independently by two authors (Yeqiong Xu and Bangshun He) according to the above inclusion and exclusion criteria. Discrep-
Table 1. Characteristics of studies included in the meta-analysis.

| Cancer type     | Year | First author | Country                      | Ethnicity | Source of control | Genotyping method | Polymorphism sites                                | Cases | Controls | HWE       |
|-----------------|------|--------------|------------------------------|-----------|-------------------|-------------------|--------------------------------------------------|-------|----------|-----------|
| Cervical cancer | 2009 | Zucchini [52] | Maton Grosso do Sul, Brazil  | African   | PB                | PCR-RFLP          | Fas -670A>G       | 91    | 176      | 0.545     |
|                 | 2008 | Tamandani [35]| Northern India               | Asian     | HB                | PCR-RFLP          | Fas -670A>G       | 200   | 200      | 0.001     |
|                 | 2008 | Kang [4]      | Korea                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 154   | 160      | 0.264, 0.233, 0.327 |
|                 | 2007 | Hvansson [53] | Sweden                       | Caucasian | PB                | TaqMan            | FasL-844C>T       | 1284  | 280      | 0.738     |
|                 | 2006 | Ueda [34]     | Japan                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G       | 83    | 95       | 0.172     |
|                 | 2005 | Zoodsma [5]   | Netherlands                  | Caucasian | PB                | TaqMan            | Fas -670A>G       | 670   | 607      | 0.274     |
|                 | 2005 | Sun [6]       | China                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 314   | 615      | 0.641, 0.304, 0.002 |
|                 | 2005 | Lai [7]       | China                        | Asian     | HB                | TaqMan            | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 318   | 318      | 0.736, 0.293, 0.920 |
|                 | 2004 | Dybikowska [8]| Poland                       | Caucasian | PB                | PCR-RFLP          | Fas -670A>G       | 314   | 615      | 0.641, 0.304, 0.002 |
|                 | 2003 | Lai [9]       | China                        | Asian     | HB                | TaqMan            | Fas -670A>G       | 176   | 176      | 0.444     |
| Gastric cancer  | 2012 | Zhang [10]    | China                        | Asian     | HB                | PCR-RFLP          | Fas -1377G>A, FasL-844C>T | 375   | 496      | 0.064, 0.112 |
|                 | 2011 | Liu [12]      | China                        | Asian     | PB                | PCR-RFLP          | Fas -1377G>A, FasL-844C>T | 344   | 324      | 0.424, 0.083 |
|                 | 2011 | Kupcinskas [11]| Mixed                       | Caucasian | PB                | TaqMan            | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 114   | 238      | 0.199, 0.492, 0.715 |
|                 | 2010 | Zhou [13]     | China                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 262   | 524      | 0.133, 0.062, 0.899 |
|                 | 2009 | Wang [14]     | China                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 332   | 324      | 0.806, 0.870, 0.554 |
|                 | 2008 | Hsu [15]      | China                        | Asian     | PB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 86    | 101      | 0.736, 0.914, 0.612 |
|                 | 2006 | Ikehara [54]  | Japan                        | Asian     | PB                | PCR-CTPP          | Fas -670A>G       | 271   | 271      | 0.504     |
| Breast cancer   | 2013 | Hashemi [16]  | Iranian                      | Caucasian | PB                | T-ARMS-PCR        | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 134   | 152      | 0.045, 0.000, 0.183 |
|                 | 2012 | Wang [17]     | China                        | Asian     | HB                | PCR-RFLP          | Fas -1377G>A, FasL-844C>T | 375   | 496      | 0.064, 0.112 |
|                 | 2012 | Mahfoudh [18] | Tunisia                      | African   | PB                | PCR-RFLP          | FasL-844C>T       | 438   | 332      | 0.334     |
|                 | 2007 | Crew [19]     | America                      | Caucasian | PB                | TaqMan            | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 1051  | 1101     | 0.754, 0.069, 0.602 |
|                 | 2007 | Zhang [20]    | China                        | Asian     | HB                | PCR-RFLP          | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 836   | 834      | 0.797, 0.700, 0.110 |
|                 | 2004 | Krippl [21]   | Austria                      | Caucasian | PB                | TaqMan            | Fas -670A>G, Fas-1377G>A, FasL-844C>T | 499   | 495      | 0.924, 0.610, 0.418 |
| Lung cancer     |      |              |                              |           |                   |                   |                                                  |       |          |           |
| Cancer type | Year  | First author | Country            | Ethnicity | Source of control | Genotyping method | Polymorphism sites | Cases | Controls | HWE      |
|------------|-------|--------------|-------------------|-----------|------------------|-------------------|--------------------|-------|----------|----------|
| Esophageal cancer | 2011 | Bye [32]    | Eastern or Western Cape | African | PB            | TaqMan          | Fas -670A>G, Fas-1377G>A, FasL -844C>T | 343   | 466      | 0.027, 0.670, 0.097 |
| Skin cancer  | 2010  | Qureshi [58] | Britain           | Caucasian | PB              | NA               | Fas -670A>G, Fas-1377G>A, FasL -844C>T | 779   | 842      | 0.210, 0.916, 0.427 |
| Ovarian cancer | 2012  | Li [62]      | China             | Asian     | PB              | Allele-specific multiple ligase detection | Fas -670A>G, Fas-1377G>A, FasL -844C>T | 342   | 344      | 0.357, 0.972, 0.547 |
| Prostate cancer | 2012  | Mandal [51]  | Northern India    | Asian     | HB              | PCR-RFLP         | Fas -670A>G, Fas-1377G>A, FasL -844C>T | 192   | 224      | 0.296, 0.035 |
| Nasopharyngeal cancer | 2008  | Lima [64]    | Portugal          | Caucasian | PB              | PCR-RFLP         | Fas -670A>G, FasL -844C>T | 657   | 247      | 0.365 |

Table 1. Cont.
Table 1. Cont.

| Cancer type     | Year | First author | Country       | Ethnicity | Source of control | Genotyping method | Polymorphism sites                                  | Cases | Controls | HWE       |
|-----------------|------|--------------|---------------|-----------|-------------------|-------------------|-----------------------------------------------------|-------|----------|-----------|
| Bladder cancer  | 2010 | Gangwar [67] | Northern India| Asian     | PB                | PCR-RFLP          | Fas-670A>G                                               | 212   | 250      | 0.384     |
|                 | 2006 | Li [68]      | China         | Asian     | HB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A, FasL-844C>T                   | 216   | 252      | 0.409, 0.970, 0.234 |
| Other cancers   | 2010 | Zhu [69]     | China         | Asian     | HB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A, FasL-844C>T                   | 333   | 365      | 0.831, 0.777, 0.278 |
|                 | 2010 | Wang [70]    | China         | Asian     | PB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A, FasL-844C>T                   | 294   | 333      | 0.034, 0.628, 0.271 |
|                 | 2008 | Yang [39]    | China         | Asian     | PB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A, FasL-844C>T                   | 397   | 907      | 0.653, 0.062, 0.986 |
|                 | 2007 | Koshkina [71]| America       | Mixed     | PB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A                                 | 123   | 510      | 0.786, 0.210 |
|                 | 2007 | Erdogan [72] | Turkey        | Caucasian | HB                | PCR-RFLP          | Fas-670A>G, FasL-844C>T                                | 45    | 100      | 0.812, 0.727 |
|                 | 2007 | Ho a [33]    | America       | Mixed     | HB                | PCR-RFLP          | Fas-1377G>A                                            | 279   | 510      | 0.210     |
|                 | 2007 | Ho b [33]    | America       | Mixed     | HB                | PCR-RFLP          | Fas-1377G>A                                            | 154   | 510      | 0.210     |
|                 | 2006 | Zhang [36]   | America       | Caucasian | HB                | PCR-RFLP          | Fas-670A>G, Fas-1377G>A, FasL-844C>T                   | 721   | 1234     | 0.481, 0.268, 0.411 |
|                 | 2006 | Ueda [34]    | Japan         | Asian     | PB                | PCR-RFLP          | Fas-670A>G                                              | 108   | 95       | 0.172     |

The Ho a investigated thyroid cancer, and the Ho b investigated salivary gland cancer.
PB: population based; HB: hospital based; T-ARMS-PCR: tetra-primer amplification refractory mutation system PCR; PCR-RFLP: restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium.

doi:10.1371/journal.pone.0090090.t001
ancies were resolved by extensive discussion in our research team. The characteristics of enrolled studies were extracted as below: the first author’s last name, year of publication, country of subjects, ethnicity, type of cancer, the source of controls, genotyping method (whether PCR was performed using a dual-labelled TaqMan probe with a specific 3’base to detect the SNPs or whether an RFLP method was used), the number of matched cases and controls, polymorphism sites, and P value for Hardy-Weinberg equilibrium (HWE) as summarized in Table 1.

Genotype-gene expression correlation analysis

The International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/) was used to obtain data of the Fas and FasL genotypes determined in 270 enrolled subjects. Meanwhile, the mRNA expression data of these enrolled subjects were available online from SNPexp (http://app3.titan.uio.no/biotools/help.php?app=snpexp) as described in the previous studies [26,27]. In brief, these data were obtained from the HapMap phase II release 23 data set consisting of 3.96 million SNP genotypes from 270 subjects of three populations, including 90 European (CEU), 90 Asian (45 Chinese, 45 Japanese), and 90 Yoruba (YRI) subjects [28]. Additionally, the mRNA expression data were derived from the lymphoblastic cell lines from the same 270 subjects [29].

Statistical analysis

Crude ORs with 95% CIs were used to assess the strength of association between the polymorphisms in Fas-670A>G, Fas-1377G>A, and FasL-844T/C and cancer risk. The pooled ORs were estimated for dominant model (variant homozygotes + heterozygous vs homozygous reference), recessive model (variant homozygotes vs heterozygous + homozygous reference), homozygote comparison (variant homozygotes vs homozygous reference), heterozygote comparison (heterozygous vs homozygous reference) and allelic comparison in the polymorphisms, respectively. Stratified analyses were performed by the type of cancer (that with only one study was grouped together as ‘other cancers’), ethnicity, source of controls and genotyping method. Heterogeneity across the studies was evaluated by using the Chi-square test based Q-statistic test, and it was considered statistically significant when P_{heterogeneity} < 0.05. The data were combined using random-effects model (the DerSimonian and Laird method) [30] in the presence of heterogeneity (P<0.05 or I^2>50%), or fixed-effects model (the Mantel-Haenszel method) models [31] was chosen to use in the absence of heterogeneity (P>0.05 or I^2<50%). Moreover, sensitivity analyses were performed to assess the stability of the results. Publication bias was evaluated graphically by using funnel plots and statistically by the Egger’s linear regression test. HWE of the three polymorphisms was assessed using a web-based program (http://ihg.gsf.de/cgi-bin/hwa1.pl). All statistical tests were performed with STATA 11.0 and SPSS 20.0. All the P values were two-sided.

Results

A total of 52 studies were enrolled in this meta-analysis (Figure 1). The major characteristics of the 52 selected studies are summarized in Table 1. The study carried out by Bye et al [32] analyzed individuals of African or Mixed ethnicity, and thus was divided into two studies. Similarly, the studies reported by Ho et al [33] and Ueda et al [34] investigated two and three types of cancer, and therefore, these two studies were cited as two studies and three studies, respectively (Table 1).

For the Fas-670A>G polymorphism, there was no association in the pooled analysis. In the subgroup analysis, statistically
significantly decreased risk was observed in prostate cancer and melanoma for GG+AG vs AA comparison model, whereas there was significantly increased risk among those of African ancestry for GG+AG vs AA models (all data shown in Table 2).

For Fas -1377G>A polymorphism, significantly increased cancer risks were observed in AA vs GG (Figure 2) and AA vs GA+GG comparison models in the overall analysis. In the subgroup analysis by cancer type, a significantly increased risk was observed in breast cancer for all comparison models. Meanwhile, increased risks were found for the comparison of AA vs GG and AA vs GA+GG in gastric cancer and esophageal cancer. In addition, a borderline decreased cancer risk was found in melanoma for GA vs GG and AA+GA vs GG comparison models (all data shown in Table 3).

For FasL -844C>T polymorphism, in the subgroup analysis of genotyping method, an increased cancer risk was found in the studies carried out by PCR-RFLP (shown in Table 4).

The Fas and FasL mRNA expression by genotypes and population

The Fas and FasL mRNA expression levels were stratified by genotype (shown in Table 5) and population (shown in Table 6) groups. In the genotype subgroup analysis, significant associations between mRNA expression levels and Fas -670A>G were observed in all populations (GA: P=0.043), especially in Asian population (GG: P=0.0003; dominant: P=0.003; recessive: P=0.001). Meanwhile, significant differences between mRNA expression levels and FasL -844C>T were observed in Asian population (recessive: P=0.001). In the population-subgroup analysis, decreased expression of Fas was found in YRI (Yoruba in Ibadan) population than in the CEU population (P=0.002).

Test of heterogeneity

There was significant heterogeneity across the studies focused on these three polymorphisms as evaluated by Q-test. Then, we evaluated the heterogeneity for dominant model comparison by subgroups (cancer type, ethnicity, source of controls and genotyping method). As a result, ethnicity ($\chi^2=13.44$, degree of freedom $=3$, $P=0.004$) and cancer type ($\chi^2=22.26$, degree of freedom $=11$, $P=0.022$), but not source of controls ($\chi^2=1.49$, degree of freedom $=1$, $P=0.222$) or genotyping method ($\chi^2=1.48$, degree of freedom $=4$, $P=0.830$) contributed to substantial heterogeneity of the Fas -670A>G polymorphism. For the Fas -1377G>A

### Table 2. Stratified analyses of the Fas -670A>G (rs1800682) polymorphism and cancer.

| Variables | n* | GG+AG vs AA | | G vs A |
| --- | --- | --- | --- | --- |
| | | OR(95%CI) | $p^b$ | $\phi^2$ | OR(95%CI) | $p^b$ | $\phi^2$ |
| **Total** | 44 | 1.01(0.94, 1.09) | <0.0001 | 47.1 | 1.04(0.96, 1.12) | 0.003 | 40.9 |
| **Cancer type** | | | | | | | |
| Cervical cancer | 9 | 1.05(0.79,1.40) | <0.0001 | 74.5 | 0.92(0.69, 1.22) | 0.006 | 62.8 |
| Gastric cancer | 5 | 1.08(0.91,1.28) | 0.340 | 11.6 | 0.97(0.79,1.21) | 0.978 | 0.0 |
| Esophageal cancer | 4 | 1.02(0.85,1.21) | 0.459 | 0.0 | 1.21(0.86,1.69) | 0.017 | 70.4 |
| Breast cancer | 4 | 1.01(0.90,1.14) | 0.325 | 13.4 | 1.03(0.90,1.18) | 0.062 | 59.1 |
| Prostate cancer | 3 | 0.83(0.70,0.98) | 0.155 | 46.4 | 0.82(0.66,1.01) | 0.346 | 5.8 |
| Ovarian cancer | 2 | 0.87(0.66,1.15) | 0.952 | 0.0 | 0.85(0.57,1.28) | 0.622 | 0.0 |
| Bladder cancer | 2 | 1.01(0.77,1.33) | 0.588 | 0.0 | 1.00(0.47,2.16) | 0.043 | 75.6 |
| Skin cancer | 2 | 1.08(0.91,1.27) | 0.414 | 0.0 | 1.02(0.86,1.23) | 0.483 | 0.0 |
| Nasopharyngeal cancer | 2 | 1.55(0.75,3.24) | 0.017 | 82.4 | 1.39(0.69,2.79) | 0.042 | 75.8 |
| Melanoma | 2 | 0.79(0.64,0.97) | 0.765 | 0.0 | 0.96(0.77,1.21) | 0.790 | 0.0 |
| Lung cancer | 2 | 0.82(0.65,1.04) | 0.852 | 0.0 | 1.07(0.82,1.40) | 0.906 | 0.0 |
| Other cancers | 7 | 1.08(0.96,1.32) | 0.737 | 3.5 | 1.15(0.99,1.32) | 0.747 | 0.0 |
| **Ethnicity** | | | | | | | |
| Asian | 25 | 0.97(0.88,1.06) | 0.004 | 48.3 | 1.01(0.89,1.15) | 0.003 | 49.3 |
| Caucasian | 13 | 1.03(0.95,1.12) | 0.120 | 32.8 | 1.00(0.92,1.09) | 0.277 | 16.5 |
| African | 3 | 1.72(1.24,2.38) | 0.288 | 19.6 | 1.23(0.78,1.95) | 0.039 | 69.1 |
| Mixed | 3 | 1.10(0.82,1.48) | 0.607 | 0.0 | 1.28(0.99,1.65) | 0.803 | 0.0 |

*aNumber of comparisons.

*bP value of Q-test for heterogeneity test.

Statistically significant results were in bold.
doi:10.1371/journal.pone.0090090.t002

For Fas -1377G>A polymorphism, significantly increased cancer risk among those of African ancestry for GG vs AA comparison model, whereas there was significantly increased risk among those of Asian ancestry for GG+AG vs AA models (all data shown in Table 2).

For Fas -1377G>A polymorphism, significantly increased cancer risks were observed in AA vs GG (Figure 2) and AA vs GA+GG comparison models in the overall analysis. In the subgroup analysis by cancer type, a significantly increased risk was observed in breast cancer for all comparison models. Meanwhile, increased risks were found for the comparison of AA vs GG and AA vs GA+GG in gastric cancer and esophageal cancer. In addition, a borderline decreased cancer risk was found in melanoma for GA vs GG and AA+GA vs GG comparison models (all data shown in Table 3).

For FasL -844C>T polymorphism, significantly increased cancer risks were observed in CC vs TT (Figure 3), CC+CT vs TT and CC vs CT+TT in the overall analysis. When the analysis was stratified by genotyping method, an increased cancer risk was observed in studies carried out by PCR-RFLP (shown in Table 4).
polymorphism, the test revealed cancer type ($\chi^2 = 22.60$, degree of freedom = 8, $P_h = 0.004$), but not ethnicity ($\chi^2 = 4.81$, degree of freedom = 3, $P_h = 0.187$), source of controls ($\chi^2 = 0.42$, degree of freedom = 1, $P_h = 0.518$), or genotyping method ($\chi^2 = 0.51$, degree of freedom = 3, $P_h = 0.917$) contributed to substantial heterogeneity. For the FasL -844C>T polymorphism, genotyping method ($\chi^2 = 9.21$, degree of freedom = 3, $P_h = 0.027$), but not cancer type ($\chi^2 = 4.33$, degree of freedom = 7, $P_h = 0.711$), ethnicity ($\chi^2 = 5.64$, degree of freedom = 3, $P_h = 0.176$) contributed to substantial heterogeneity.

Figure 2. Forest plots of effect estimates for Fas-1377G>A polymorphism (AA vs GG). For each of the studies, the estimation of OR and its 95% CI is plotted with a box and a horizontal line. Filled diamond pooled OR and its 95% CI.

doi:10.1371/journal.pone.0090090.g002

Association of Fas/FasL Polymorphisms with Cancer
### Table 3. Stratified analyses of the Fas -1377G>A (rs2234767) polymorphism and cancer.

| Variables                | n   | AA vs GG          | OR(95%CI)     | p^b  | I^2  | AA vs GG          | OR(95%CI)     | p^b  | I^2  | AA vs GA+GG       | OR(95%CI)     | p^b  | I^2  | A vs G           | OR(95%CI)     | p^b  |
|--------------------------|-----|-------------------|---------------|------|------|-------------------|---------------|------|------|-------------------|---------------|------|------|-----------------|---------------|------|
| Total                    | 37  | 1.19(1.06, 1.34)  | 0.024         | 34.7 | 1     | 1.00(0.94,1.06)  | 0.033         | 32.2 | 0.012 | 1.03(0.97,1.10)  | 0.012         | 37.8 | 0.002 | 1.21(1.09, 1.34) | 0.048         | 30.3 |
| Cancer type              |     |                   |               |      |      |                   |               |      |      |                   |               |      |      |                 |               |      |
| Gastric cancer           | 6   | 1.31(1.05, 1.65)  | 0.934         | 0.0  | 0.99 | 0.99(0.85,1.14)  | 0.810         | 0.0  | 0.0  | 1.04(0.91,1.20)  | 0.659         | 0.0  | 0.0  | 1.32(1.07,1.64)  | 0.328         | 13.6 |
| Breast cancer            | 5   | 1.39(1.12,1.72)   | 0.420         | 0.0  | 0.263 | 1.15(1.02,1.30)  | 0.246         | 26.3 | 0.0  | 1.18(1.06,1.32)  | 0.233         | 25.3 | 0.0  | 1.28(1.05,1.56)  | 0.236         | 27.8 |
| Lung cancer              | 4   | 1.18(0.82,1.70)   | 0.050         | 66.6 | 0.743 | 0.97(0.87,1.08)  | 0.743         | 0.0  | 0.0  | 1.01(0.91,1.12)  | 0.687         | 0.0  | 0.0  | 1.23(0.86,1.74)  | 0.044         | 68.0 |
| Esophageal cancer        | 3   | 1.42(1.03,1.96)   | 0.106         | 55.4 | 0.031 | 0.96(0.66,1.37)  | 0.031         | 71.2 | 0.0  | 1.00(0.72,1.39)  | 0.043         | 68.1 | 0.0  | 1.58(1.16,2.13)  | 0.089         | 58.7 |
| Cervical cancer          | 3   | 0.95(0.70,1.28)   | 0.201         | 37.6 | 0.149 | 0.85(0.70,1.04)  | 0.149         | 47.4 | 0.0  | 0.88(0.73,1.06)  | 0.165         | 44.6 | 0.0  | 1.08(0.81,1.42)  | 0.215         | 35.0 |
| Prostate cancer          | 2   | 0.82(0.61,1.10)   | 0.199         | 39.5 | 0.042 | 0.91(0.53,1.54)  | 0.042         | 75.9 | 0.0  | 0.90(0.54,1.50)  | 0.042         | 75.8 | 0.0  | 0.91(0.70,1.19)  | 0.698         | 0.0  |
| Ovarian cancer           | 2   | 0.91(0.54,1.52)   | NA            | NA   | 0.286 | 1.04(0.77,1.40)  | 1.02(0.77,1.36) | 12.1 | 0.0  | 0.91(0.56,1.50)  | NA            | NA   | 0.0  | 1.00(0.80,1.24)  | 0.308         | 3.8  |
| Melanoma                 | 2   | 0.74(0.37,1.46)   | 0.645         | 0.0  | 0.614 | 0.79(0.62,1.00)  | 0.614         | 0.0  | 0.0  | 0.78(0.62,0.98)  | 0.748         | 0.0  | 0.0  | 0.77(0.39,1.52)  | 0.617         | 0.0  |
| Other cancers            | 10  | 1.32(1.12,1.56)   | 0.327         | 12.5 | 0.437 | 1.07(0.97,1.17)  | 0.437         | 8.5  | 0.0  | 1.10(1.01,1.21)  | 0.364         | 8.5  | 0.0  | 1.28(1.10,1.49)  | 0.351         | 10.0 |

*aNumber of comparisons.  
^bP value of Q-test for heterogeneity test.  
^cRandom-effect model was applied when P value for heterogeneity <0.05; otherwise, fixed-effect model was applied.  
Statistically significant results were in bold.

doi:10.1371/journal.pone.0090090.t003
degree of freedom = 3, \( P = 0.131 \), or source of controls (\( \chi^2 = 0.08 \), degree of freedom = 1, \( P = 0.777 \)) contributed to substantial heterogeneity.

Sensitivity analyses

To assess the stability of the results and the source of the heterogeneity, sensitivity analysis was performed by sequential removal of each individual eligible study. For \( Fas \)-670A>G and \( FasL \)-844C>T polymorphisms, statistically similar results were observed after sequential removal of individual study in dominant and homozygote model, respectively, and the summary ORs in the other genetic models were not materially altered, suggesting that the results were stable. For the \( Fas \)-1377G>A polymorphism, sensitivity analysis indicated that study by Shao et al [38] was
responsible for heterogeneity. The heterogeneity was decreased when this study was removed (AA+GA vs GG: $P_h=0.075$, $I^2=26.5$). Although the genotype distribution in 11 studies (listed in Table 1) didn’t follow HWE, the corresponding summary ORs were not materially altered with or without including these studies for the three polymorphisms. In addition, no other single study altered the pooled ORs by sensitivity analysis.

Publication bias

To assess the publication bias, Begg’s funnel plot and Egger’s test were performed and the shapes of funnel plots didn’t show any obvious asymmetry in all genetic models of the three polymorphisms (Figure 4A–C). Therefore, to provide statistical evidence of funnel plot symmetry, Egger’s test was performed for each of these polymorphisms and the results confirmed the absence of publication bias ($P>0.05$).

Discussion

Fas, a potent member of the death receptor family, plays a crucial role in apoptotic signaling in many cell types [40]. Meanwhile, interactions between Fas and its receptor FasL trigger the death signal cascade, and subsequently induce apoptotic cell death [41]. Previous studies have indicated that down-regulation of Fas expression and/or up-regulation of FasL expression could be detected in many types of human tumors [42,43]. The reason may be that down-regulation of Fas could protect tumor cells from elimination by anti-tumor immune responses, whereas up-regulation of FasL could increase the ability of tumor cells to counterattack the immune system by inducing apoptosis [44,45,46]. Therefore, it is believed that Fas and FasL play a crucial role in carcinogenesis. Given the important roles of Fas and FasL in carcinogenesis process, it is biologically plausible that Fas and FasL polymorphisms that possess the potential to influence the expression of Fas and/or FasL may be associated with cancer risk. Therefore, associations between the Fas -670A>G, Fas -1377G>A and FasL -844C>T polymorphisms and cancer risk were determined in this meta-analysis.

In this meta-analysis, 52 published studies were enrolled to determine the association between the three potentially functional polymorphisms within the Fas and FasL and cancer risk. This study revealed that the Fas -1377G>A and FasL -844C>T, but not the Fas -670A>G polymorphisms were associated with significantly increased overall cancer risk. Previous studies have identified that the -1377A allele had markedly reduced ability to bind transcription factor stimulatory protein 1 as compared with the -1377G allele, whereas the -670A and G alleles had similar ability to bind transcription factor signal transducers and activators of transcription 1 (STAT1)[47]. As the Fas -1377A allele reduced the ability to bind transcription factor stimulatory protein 1 that is a crucial transcriptional activator, the expression of Fas was decreased in carriers of the Fas -1377AA genotype as expected, but the Fas -670G allele didn’t influence the expression of Fas [47,48]. Therefore, it is reasonable that the Fas -1377A allele increased the overall cancer risk, and that the Fas -670G allele had no marked effect on overall cancer risk, which was consistent with our results. For the FasL -844T>C polymorphism, which is located in a binding motif for transcription factor CAAT/enhancer binding protein $\beta$, could influence the promoter activity of the FasL gene [49]. Additionally, it has been proposed that compared with the -844T allele, -844G allele strongly increased the expression of FasL on T cells and was associated with an enhanced rate of activation-induced cell death of T cells, which may lead to less powerful immune surveillance and increase the susceptibility to cancer [6].
The Fas -670GG genotype was associated with decreased risk of prostate cancer and melanoma according to the cancer type subgroup analysis. It was suggested that Fas -670A>G polymorphism might have the same effect on these two cancers. However, these results were based on 44 studies, which could affect the results owing to small amount of studies. Therefore, to draw a more precise conclusion, more related studies are needed.

For the Fas -1377G>A polymorphism, this study revealed that those who carried the -1377AA genotype had an increased risk for breast cancer, gastric cancer and esophageal cancer, while the melanoma risk was decreased. As described above, the different risk factors could contribute to the discrepancies. Also other unidentified causal genes would influence the effect of this polymorphism on different cancers.

For the FasL -844C>T polymorphism, the -844CC associated with increased cancer risk was observed in gastric cancer, esophageal cancer, and ovarian cancer among the previous studies, indicating that this polymorphism had similar effect on these three cancers. Although these cancers had different mechanisms of carcinogenesis, small amount of studies, publication bias, and other unidentified causal genes would be the result of the discrepancies, which contributed to the similar association between the FasL -844C>T polymorphism and three cancers.

In the subgroup analysis by ethnicity, an increased cancer risk in carriers of the Fas -670GG genotype was found in African, while the result of mRNA expression showed that GG genotype expressed higher levels of Fas in Asian populations. Meanwhile, the previous studies showed increased cancer risk in carriers of the Fas -1377AA and FasL -844CC genotype were found in Asian subjects, which was evidenced in mRNA expression by genotypes.

Table 5. Fas and FasL mRNA expression by the genotypes of SNPs, using data from the HapMap.

| Fas -670A>G | FasL -844C>T |
|-----------|-------------|
| Population | Genotypes | No. | Mean ± SD | P² | Ethnicity | Genotypes | No. | Mean ± SD | P² |
| CEU² | AA | 23 | 8.79±0.36 | | CEU² | CC | 76 | 5.94±0.07 | |
| | GA | 46 | 8.87±0.28 | 0.321 | | CT | 5 | 5.89±0.07 | 0.137 |
| | GG | 12 | 8.74±0.36 | 0.687 | | TT | 0 | — | — |
| | Dominant | 58 | 8.84±0.30 | 0.511 | | Dominant | 5 | 5.89±0.07 | 0.137 |
| | Recessive | 69 | 8.84±0.31 | 0.292 | | Recessive | 81 | — | — |
| YRI² | AA | 6 | 8.58±0.33 | | YRI² | CC | 0 | — | — |
| | GA | 25 | 8.70±0.31 | 0.402 | | CT | 28 | 5.94±0.06 | — |
| | GG | 53 | 8.67±0.30 | 0.450 | | TT | 53 | 5.95±0.06 | — |
| | Dominant | 78 | 8.58±0.33 | 0.410 | | Dominant | 81 | 5.95±0.06 | — |
| | Recessive | 31 | 8.67±0.31 | 0.987 | | Recessive | 28 | 5.94±0.06 | 0.493 |
| Asian² | AA | 28 | 8.65±0.29 | | Asian² | CC | 0 | — | — |
| | GA | 36 | 8.78±0.26 | 0.059 | | CT | 50 | 5.96±0.06 | — |
| | GG | 21 | 8.98±0.30 | 0.0003 | | TT | 33 | 5.91±0.06 | — |
| | Dominant | 57 | 8.85±0.29 | 0.003 | | Dominant | 83 | 5.94±0.06 | — |
| | Recessive | 64 | 8.72±0.28 | 0.001 | | Recessive | 50 | 5.96±0.06 | 0.001 |
| All² | AA | 57 | 8.70±0.33 | | All² | CC | 76 | 5.94±0.07 | — |
| | GA | 107 | 8.80±0.28 | 0.043 | | CT | 83 | 5.95±0.06 | 0.163 |
| | GG | 86 | 8.76±0.33 | 0.297 | | TT | 86 | 5.94±0.06 | 0.913 |
| | Dominant | 193 | 8.78±0.30 | 0.081 | | Dominant | 169 | 5.95±0.06 | 0.390 |
| | Recessive | 164 | 8.76±0.30 | 0.871 | | Recessive | 159 | 5.95±0.06 | <0.0001 |

CEU: 90 Utah residents with ancestry from northern and western Europe; YRI: 90 Yoruba in Ibadan, Nigeria; Asian: 45 unrelated Han Chinese in Beijing and 45 unrelated Japanese in Tokyo.

²Genotyping data and mRNA expression levels for Fas and FasL by genotypes were obtained from the HapMap phase II release 23 data from EBV-transformed lymphoblastoid cell lines from 270 individuals.

²Two-side Student's t test within the stratum was used.

Table 6. Fas and FasL mRNA expression by the ethnicity, using data from the HapMap.

| Fas -670A>G | FasL -844C>T |
|-----------|-------------|
| Ethnicity | No. | Mean ± SD | | Ethnicity | No. | Mean ± SD |
| CEU² | 81 | 8.83±0.31 | | CEU² | 81 | 5.94±0.07 |
| YRI² | 84 | 8.67±0.30 | 0.002 | YRI² | 81 | 5.95±0.06 | 0.120 |
| Asian² | 85 | 8.79±0.30 | 0.391 | Asian² | 83 | 5.94±0.06 | 0.398 |

CEU: 90 Utah residents with ancestry from northern and western Europe; YRI: 90 Yoruba in Ibadan, Nigeria; Asian: 45 unrelated Han Chinese in Beijing and 45 unrelated Japanese in Tokyo.

¹Genotyping data and mRNA expression levels for Fas and FasL by genotypes were obtained from the HapMap phase II release 23 data from EBV-transformed lymphoblastoid cell lines from 270 individuals.

²Two-side Student's t test within the stratum was used.

There were missing data for unavailable genotyping data.

Statistically significant results were in bold.

doi:10.1371/journal.pone.0090090.t005

doi:10.1371/journal.pone.0090090.t006

doi:10.1371/journal.pone.0090090.t007

doi:10.1371/journal.pone.0090090.t008

doi:10.1371/journal.pone.0090090.t009
in Asian populations. However, this association was not proved in other ethnicities. The discrepancies in racial backgrounds and environment they lived in would lead to the differences. In addition, these polymorphisms might be masked by the presence of other unidentified causal genes involved in carcinogenesis. Due to the small size of population for the ethnicities, well-designed, large randomized case-control studies should be performed.

The pooled results of this study may be affected by polymorphism genotyping methods applied in the enrolled studies. Previous studies revealed that the pooled results of the Fas -670A>G polymorphism were not affected by the studies with genotyping methods of both PCR-RFLP and TaqMan. While Fas -1377AA genotype carriers increased cancer risk in the studies using PCR-RFLP but not TaqMan, and similar result was found in the Fasl -844CC genotype carrier. The discrepancy across the studies applied different polymorphism genotyping methods may result from the different sensitivity and accuracy of genotyping methods. Meanwhile, the quality control is crucial to cause discrepancy as well. In general, studies [12,17,50] selected 10% repeated, random sample of subjects to test twice by standard genotyping method or different investigator, which was used to confirm the accuracy of results, while Mandal et al [51] and Ter-Minassian et al [22] tested 5% repeated samples. As a result, the consistency rate of quality control was 100% in almost all studies. However, the study by Crew et al [19] showed that the consistency rate was 100% for Fas -1377G>A, 94% for Fas -670G>A and 96% for Fasl -844G>T. Therefore, the results of further studies should be confirmed by a standardized genotyping method. In addition, the limited amount of studies would also contribute to the discrepancy.

Heterogeneity is an important factor which can interpret the results of the meta-analysis. Therefore, we stratified the studies by cancer type, ethnicity, source of controls and genotyping method, respectively. The results showed that the main heterogeneity existed for cancer type and ethnicity. The reason might be that geographic differences, exposure of the Sun, eating habits, and environmental pollutants could exist in different ethnicities, which contributed to the heterogeneity.

Some limitations of the meta-analysis should be addressed. First, only studies in English were enrolled in this meta-analysis, which might miss some studies in other languages consistent with inclusion criteria. Second, some eligible studies included in the meta-analysis were hospital-based controls, which could generate the selection bias. Third, only a limited amount of studies was included, which might limit the strength of the associations. Finally, some suspected factors such as drinking, smoking, age, sex, and living habits were not considered in the meta-analysis. Regardless of such limitations, this meta-analysis still had some strengths. We investigated heterogeneity that may result from ethnicity of subjects, the types of cancer, the source of control subjects, and various genotyping methods. In addition, we analyzed the relationship between the mRNA expressions and genotypes, which partly supported the results of this meta-analysis.

In summary, this meta-analysis indicates that the Fas-1377G>A and Fasl -844T/C polymorphisms are associated with increased cancer risk, but that no significant association is observed for the Fas -670A>G polymorphism and cancer risk. A definite conclusion should be made in the future through well-designed, unbiased, powered, population-based case-control association studies.

Supporting Information

CHECKLIST S1 | PRISMA Checklist.

Author Contributions

Conceived and designed the experiments: SKW YQX BSH. Performed the experiments: YQX RL YQP GQS TYG QWD HLS. Analyzed the data: BSH YQX. Contributed reagents/materials/analysis tools: RL YQX. Wrote the paper: SKW YQX BSH RL.

Association of Fas/Fasl Polymorphisms with Cancer

Figure 4. Begg’s funnel plot of Egger’s test for publication bias for three polymorphisms. Each circle represents as an independent study for the indicated association. Log(OH), natural logarithm of OR. Horizontal lines mean effect size. A: Begg’s funnel plot of publication bias test for Fas -670A>G polymorphism. B: Begg’s funnel plot of publication bias test for Fas -1377G>A polymorphism. C: Begg’s funnel plot of publication bias test for Fasl -844C>T polymorphism.

doi:10.1371/journal.pone.0090090.g004

References

1. Lichtenstein P, Holm NV, Verkasalo PK, Liadou A, Kaprio J, et al. (2000) Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343: 78-85.
2. Itoh N, Yonehara S, Ishii A, Yonehara M, Mizushima S, et al. (1991) The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis. Cell 66: 233-243.
3. Ohnuma A, Behrmann I, Falk W, Pasilita M, Maier G, et al. (1992) Purification and molecular cloning of the APO-1 cell surface antigen, a member of the tumor necrosis factor/receptor superfamily. Sequence identity with the Fas antigen. J Biol Chem 267: 10709–10715.
4. Kang S, Dong SM, Seo SS, Shim JW, Park SY (2008) FAS -1377 G/A polymorphism and the risk of lymph node metastasis in cervical cancer. Cancer Genet Cytogenet 180: 1–5.
5. Zoulima M, Neile IM, Schipper M, Oosterom E, van der Steege G, et al. (2005) Interleukin-10 and Fas: polymorphisms and susceptibility for [pre]neoplastic cervical disease. Int J Gynecol Cancer 15 Suppl 3: 282–296.
6. Sun T, Zhou Y, Li H, Han X, Shi Y, et al. (2005) FASL -844C polymorphism is associated with increased activation-induced T cell death and risk of cervical cancer. J Exp Med 202: 967–974.
7. Liu HC, Lin WY, Lin YW, Chang CC, Yu MH, et al. (2005) Genetic polymorphisms of FAS and FASL (CD95/CD95L) genes in cervical carcinoma. Carcinogenesis: An analysis of haplotype and gene-gene interaction. Gynecol Oncol 99: 113–118.
8. Dybikowska A, Slivinski W, Emeric J, Podhajska AJ (2000) Evaluation of Fas gene promoter polymorphism in cervical cancer patients. Int J Mol Med 14: 475–478.
9. Lai HC, Sytwu HK, Sun CA, Yu MH, Yu CP, et al. (2003) Single nucleotide polymorphism at Fas promoter is associated with cervical carcinogenesis. Jpn J Cancer Res 104: 221–225.
10. Zhang W, Li C, Wang J, He J (2012) Functional polymorphisms in FAS/FASL system contribute to the risk of occurrence but not progression of gastric cardiac adenocarcinoma. Hepatogastroenterology 59: 141–146.
11. Kupcinets J, Wes T, Bornschein J, Solgrad M, Leja M, et al. (2011) Lack of association between gene polymorphisms of Angiotensin converting enzyme, Nod-like receptor 1, Toll-like receptor 4, FAS/FASL and the presence of Helicobacter pylori-induced premalignant gastric lesions and gastric cancer in Czeckian. BMC Med Genet 12: 112.
12. Liu L, Wu C, Wang Y, Zhong R, Wang F, et al. (2011) Association of candidate genetic variants with gastric cardia adenocarcinoma in Chinese population: a multiple interaction analysis. Carcinogenesis 32: 336–342.
13. Zhou RM, Wang N, Chen ZF, Duan YM, Sun DL, et al. (2010) Polymorphisms in promoter region of FAS and FASL gene and risk of cardia gastric adenocarcinoma. J Gastroenterol Hepatol 25: 555–561.
40. Andera L (2009) Signaling activated by the death receptors of the TNFR family.

39. Yang M, Sun T, Wang L, Yu D, Zhang X, et al. (2008) Functional variants in

37. Bel Hadj Jrad B, Mahfouth W, Bouaouina N, Gabbouj S, Ahmed SB, et al. (2012) Polymorphisms of the FAS and FASL gene and risk of prostate cancer. Clin Cancer Res 18: 2548-2551.

36. Zhang Z, Wang LE, Sturgis EM, El-Naggar AK, Hong WK, et al. (2006) A polymorphism in FAS gene promoter associated with increased risk of oral cancer and FASL gene polymorphism: A biomarker for the metastasis of nasopharyngeal carcinoma. J Natl Cancer Inst 96: 1030-1036.

35. Wu J, Metz C, Xu X, Abe R, Gibson AW, et al. (2003) A novel polymorphic CAAT/enhancer-binding protein beta element in the Fas, gene promoter alters Fas ligand expression: a candidate background gene in African American systemic lupus erythematosus patients. J Immunol 170: 132-138.

34. Ueda M, Terai Y, Kanda K, Kanemura M, Takehara M, et al. (2006) Fas gene polymorphism with risk of oral cancer and FASL gene polymorphism: a biomarker of good prognosis of breast cancer in the Tunisian population. Hum Immunol 73: 932-938.

33. Zucchi F, da Silva ID, Ribalta JC, de Souza NC, Speck NM, et al. (2009) Fas/CD95 promoter polymorphism gene and its relationship with cervical dysplasia and cervical cancer. Tumour Biol 30: 142-144.

32. Ivanovska JM, Magussun JJ, Steiner LL, Magussun PK, et al. (2007) Variants of chemokine receptor 2 and interleukin 4 receptor, but not interleukin 10 or Fas ligand, increase risk of cervical cancer. Int J Cancer 121: 2445-2457.

31. Behar KA, Behar Y, Matsu K, Hirose K, Niwa T, et al. (2006) 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 51: 927-931.

30. Wang B, Sun T, Xue L, Han X, Lu N, et al. (2007) Functional polymorphisms of FAS and FASL genes and risk of prostate cancer in a Chinese population. Urol Oncol 30: 555-561.

29. Zhang X, Miao X, Sun T, Tan W, Qi S, et al. (2005) Functional polymorphisms in the XPG gene and risk of non-melanoma skin cancer. Carcinogenesis 26: 1235-1244.

28. (2003) The International HapMap Project. Nature 426: 789–796.

27. Park SH, Choi JE, Kim EJ, Jang JS, Lee WK, et al. (2006) Polymorphisms in the FAS gene promoter and risk of cervical cancer. Jpn J Cancer Res 97: 991-993.

26. Wang W, Zheng Z, Yu W, Lin H, Cui B, et al. (2012) Polymorphisms of the FAS gene promoter and risk of prostate cancer in Chinese population. Urology 80: 2281–2291.

25. Zhang X, Miao X, Sun T, Tan W, Qi S, et al. (2005) Functional polymorphisms of the FAS and FASL genes and risk of prostate cancer. Clin Cancer Res 11: 2579-2586.

24. Park SH, Choi JE, Kim EJ, Jang JS, Lee WK, et al. (2006) Polymorphisms in the FAS gene promoter and risk of cervical cancer. Jpn J Cancer Res 97: 991-993.

23. Wang M, Wu D, Tan M, Gong W, Xue H, et al. (2009) FAS and FAS ligand polymorphisms in the promoter regions and risk of gastric cancer in Southern China. Biochem Genet 47: 559-568.

22. Byer H, Prescott NJ, Matejic M, Rose E, Lewis CM, et al. (2011) Population-specific genetic associations with oesophageal squamous cell carcinoma in South Africa. Carcinogenesis 32: 1053–1061.

21. Ho T, Li G, Zhao C, Zheng R, Wei Q, et al. (2008) Fas single nucleotide polymorphism is associated with risk of thyroid and salivary gland carcinomas: a case-control analysis. Head Neck 30: 297–305.

20. Zhang B, Sun T, Xue L, Han X, Lu N, et al. (2007) Functional polymorphisms in FAS and FASL contribute to increased apoptosis of tumor infiltration lymphocytes and risk of breast cancer. Carcinogenesis 28: 1067–1073.

19. Krippel P, Langenbeuler U, Reiner W, Koppel H, Samonig H (2004) Re: Polymorphisms of death pathway genes FAS and FASL in esophageal squamous-cell carcinoma. J Natl Cancer Inst 96: 1478–1479; reply 1479.

18. Ter-Minassian M, Zhai R, Assoumou K, Su L, Zhou W, et al. (2008) Apoptosis gene polymorphisms, age, smoking and the risk of non-small cell lung cancer. Carcinogenesis 29: 2147–2152.

17. Wang W, Zheng Z, Yu W, Lin H, Cui B, et al. (2007) Fas A670G polymorphism, CCND1 (G870A) and FAS (A-670G) polymorphisms in bladder cancer risk. Prostate Cancer Prostatic Dis 10: 94–98.

16. Bel Hadj Jrad B, Mahfouth W, Bouaouina N, Gabbouj S, Ahmed SB, et al. (2012) Polymorphisms of the FAS and FASL gene and risk of prostate cancer in a Korean population. Lung Cancer 54: 303–308.

15. Hsu PI, Lu PJ, Wang EM, Ger LP, Lo GH, et al. (2008) Polymorphisms of death pathway genes FAS and FASL and risk of prostate cancer. Jpn J Cancer Res 99: 454–460.

14. Wang M, Wu D, Tan M, Gong W, Xue H, et al. (2009) Fas-fas ligand-induced apoptosis as a mechanism of immune privilege. Science 270: 1109–1112.

13. Strand S, Hofmann WJ, Hug H, Muller M, Otto G, et al. (1996) Lymphocyte apoptosis induced by CD95 (APO-1/Fas) ligand-expressing tumor cells—a mechanism of immune evasion? Nat Med 2: 1361–1366.

12. Reichmann E (2002) The biological role of the Fas/Fasl system during tumor formation and progression. Semin Cancer Biol 12: 309–315.

11. Sloky J, Rollinson S, Allan JM, Smith AG, Law GR, et al. (2003) Functional FAS promoter polymorphisms are associated with increased risk of acute myeloid leukemia. Cancer Res 63: 4327–4330.

10. Huang QR, Morris D, Manolios N (1997) Identification and characterization of polymorphisms in the promoter region of the human Apo-1/CD95 gene. Mol Immunol 34: 577–582.

9. Wu J, Metz C, Xu X, Abe R, Gibson AW, et al. (2003) A novel polymorphic CAAT/enhancer-binding protein beta element in the Fas, gene promoter alters Fas ligand expression: a candidate background gene in African American systemic lupus erythematosus patients. J Immunol 170: 132-138.

8. Shao P, Ding Q, Qin C, Wang M, Tang J, et al. (2011) Functional polymorphisms in cell death pathway genes FAS and FAS ligand and risk of prostate cancer in a Chinese population. Prostate 71: 341–342.

7. Mandle RK, Mittal RD (2007) Fas ligand cell cycle and apoptosis associated with prostate cancer risk in North Indian population? Urol Oncol 30: 555-561.

6. Zhu Q, Wang T, Ren J, Hu K, Liu W, et al. (2010) FAS-670A/G polymorphism: a biomarker for the metastasis of nasopharyngeal carcinoma. J Natl Cancer Inst 96: 1030-1036.

5. Qureshi A, Nan H, Dyer M, Han J (2010) Polymorphisms of FAS and FAS ligand genes and risk of skin cancer. J Dermatol Sci 58: 78–80.

4. Zhang H, Sun XF, Symrortudt J, Redahl I (2007) Importance of FAS-1377, FAS-L and FASL-844 T/C gene polymorphisms and epithelial ovarian cancer. Clin Chim Acta 411: 584–589.

3. Czene-Grac-Jurcevic T, Eshlimou C, Capelli P, Blaveri E, Baron A, et al. (2001) Gene expression profiles of pancreatic cancer and stromal desmolysoma. Oncogene 20: 7437–7446.

2. Griffith TS, Brunner T, Fletcher SM, Green DR, Ferguson TA (1993) Fas ligand-induced apoptosis as a mechanism of immune privilege. Science 270: 1109–1112.

1. Strand S, Hofmann WJ, Hug H, Muller M, Otto G, et al. (1996) Lymphocyte apoptosis induced by CD95 (APO-1/Fas) ligand-expressing tumor cells—a mechanism of immune evasion? Nat Med 2: 1361–1366.
malignant potential of oral premalignant lesions in a Taiwanese population. J Oral Pathol Med 39: 155–161.

71. Koshkina NV, Kleinerman ES, Li G, Zhao CC, Wei Q, et al. (2007) Exploratory analysis of Fas gene polymorphisms in pediatric osteosarcoma patients. J Pediatr Hematol Oncol 29: 815–821.

72. Erdogan M, Karadeniz M, Berdeli A, Tamsel S, Ertan Y, et al. (2007) Fas/Fas ligand gene polymorphism in patients with papillary thyroid cancer in the Turkish population. J Endocrinol Invest 30: 411–416.