The SDF-1 rs1801157 Polymorphism is Associated with Cancer Risk: An Update Pooled Analysis and FPRP Test of 17,876 Participants

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The stromal cell derived factor-1 (SDF-1) rs1801157 gene polymorphism has been implicated in susceptibility to cancer, but the results were inconclusive. The current study was to precisely investigate the association between SDF-1 rs1801157 polymorphism and cancer risk using meta-analysis and the false positive report probability (FPRP) test. All 17,876 participants were included in the study. The meta-analysis results indicated a significant association between the SDF-1 rs1801157 polymorphism and cancer risk. By subgroup analyses, the results detected that the SDF-1 rs1801157 polymorphism was associated with cancer susceptibility among Asians and Caucasians. Additionally, we also found significant associations between the SDF-1 rs1801157 polymorphism and susceptibility to different types of cancer. However, to avoid a “false positive report”, we further investigated the significant associations observed in the present meta-analysis using the FPRP test. Interestingly, the results of the FPRP test indicated that only 4 gene models were truly associated with cancer risk, especially in Asians. Moreover, we confirmed that the SDF-1 rs1801157 gene polymorphism was only associated with lung and urologic cancer risk. In summary, this study suggested that the SDF-1 rs1801157 polymorphism may serve as a risk factor for cancer development among Asians, especially an increased risk of urologic and lung cancers.

Cancer remains a major cause of mortality worldwide. It is estimated that the cancer death rate will be increased by 5-fold in developing countries, and the global cancer mortality is expected to increase by 104% in 2020⁶. Cancer is a multi-factorial disease that results from complex interactions between numerous genetic and environmental factors⁴. In recent years, an increasing number of studies has focused on the association between chemokine gene variants and malignancy susceptibility. Among them, the stromal cell derived factor-1 (SDF-1) gene, also known as CXC chemokine ligand 12 (CXCL12), has been widely studied⁴–⁶. The SDF-1 gene is located on chromosome 10q11.1 and spans 10 kb⁷. The SDF-1 gene mainly encodes a CXC angiogenic chemokine⁸. One important SDF-1 gene polymorphism named rs1801157 (G801A) involves a guanine to adenine (G→C) substitution at base pair 801 of the 3′-untranslated region of SDF-1 gene⁹.

Previous studies have indicated that SDF-1 participates in several biological activities, including neuronal and cardiogenesis development, haematopoiesis and lymphocyte trafficking¹⁰. Furthermore, growing evidence suggests that the SDF-1 rs1801157 polymorphism plays an important role in the pathogenesis of cancer. Razmkhah et al. reported that the SDF-1 rs1801157 polymorphism increased the risk of breast and lung cancer¹¹,¹². Kucukgergin and co-workers showed that the SDF-1 rs1801157 polymorphism was associated with bladder cancer susceptibility¹³. Hirata et al. reported that the SDF-1 rs1801157 polymorphism is potentially associated with an increased risk of prostate cancer among Japanese individuals¹⁴. However, Petersen et al. did not identify an association between the SDF-1 rs1801157 polymorphism and prostate cancer susceptibility¹⁵, and similar negative results were also detected by Tee and colleagues¹⁶.
The results of those genetic association studies were inconclusive. Moreover, a single study may be insufficient to detect a small effect of the SDF-1 rs1801157 gene polymorphism on cancer susceptibility, especially when the sample size is relatively small. Considering the crucial role of the SDF-1 rs1801157 gene polymorphism in the pathogenesis of cancer, we performed a meta-analysis to accurately investigate the association of the SDF-1 rs1801157 gene polymorphism with cancer risk. Furthermore, to avoid a “false positive report”, we further assessed the significant associations observed in the present meta-analysis using the false positive report probability (FPRP) test. To our knowledge, this study is most recent and accurate meta-analysis exploring the SDF-1 rs1801157 gene polymorphism in cancer susceptibility.

Results
Study characteristics. As indicated in the flow diagram (Fig. 1), 247 articles were identified after an initial search. After reading the titles and abstracts, we excluded 198 articles. The remaining 49 articles were further screened by a full-text review. Six articles were excluded because they investigated other SDF-1 gene polymorphisms (e.g., rs2839693 and rs1065297) rather than the rs1801157 polymorphism. Four articles were excluded because they were not case-control studies. One article was not included because it was a meta-analysis, and one article was excluded because the available data could not be extracted to further assess the effect size. Therefore, all 37 articles were identified 4–6,11–44. However, according to the results of the HWE test, 4 articles 18,38,39,44 were excluded because they did not achieve HWE in the control group. Finally, a total of 34 eligible case-control studies from 33 articles4–6,11–17,19–37,40–43 were included in the study. Among them, 18 articles were performed on Caucasians4,6,15,17,19–24,27–29,31,33,34,40,43, 13 articles on Asians5,11–14,16,25,26,30,32,35–37, and two studies on individuals of mixed ethnicity41,42. In addition, based on the quality score, eleven studies were considered low quality. The characteristics of included studies are summarized in Tables 1 and 2.

Meta-analysis results. In total, 17,876 participants (8,062 cases and 9,814 controls) from 34 case-control studies were included in the current meta-analysis assessing the relationship between the SDF-1 rs1801157 polymorphism and cancer risk. In the overall meta-analysis, the results suggested a significant association between the SDF-1 rs1801157 polymorphism and cancer susceptibility in the recessive model (AA vs. AG + GG, OR: 1.28, 95% CI: 1.11–1.47, P = 0.001), a co-dominant model (AA vs. GG, OR: 1.43, 95% CI: 1.24–1.65, P < 0.001) as assessed by a fixed-effect model (I² = 47%, 49.7%, respectively) and other models (AA + AG vs. GG, OR: 1.33, 95% CI: 1.17–1.51, P < 0.001; AG vs. GG, OR: 1.35, 95% CI: 1.19–1.54, P < 0.001; A vs. G, OR: 1.26, 95% CI: 1.14–1.40, P < 0.001) (Figs 2 and 3) as assessed by a random-effect model (I² = 70.8%, 66.4%, 69.5%, respectively) (Table 3).

In the subgroup analyses of ethnicity, the meta-analysis results indicated a strong association between the SDF-1 rs1801157 polymorphism and cancer susceptibility among Asians (AA + AG vs. GG, OR: 1.63, 95% CI: 1.34–1.98, P < 0.001) and a weak association in Caucasians (AG vs. GG, OR: 1.10, 95% CI: 1.00–1.21, P = 0.05), but no association in mixed populations using different genetic models (Table 3). Additionally, we also conducted subgroup analyses of cancer types. As shown in Table 3, significant associations between the SDF-1 rs1801157 polymorphism and breast cancer, urologic cancer, hematologic malignancy and lung cancer susceptibility were found in different genetic models. However, no association was observed between the SDF-1 rs1801157 polymorphism and risk of head and neck cancer, gynecological cancer and digestive system cancer (Table 3).

Publication bias and sensitivity analysis. The funnel plot is a symmetrical inverted funnel (Fig. 4). No publication biases were noted using Begg’s (P = 0.329) and Egger’s tests (P = 0.082). Additionally, to further investigate the possible source of heterogeneity, we executed a sensitivity analysis by sequentially excluding studies from the meta-analysis to investigate the influence of each study on the pooled results. The sensitivity analysis results reported that the pooled ORs were not materially altered, suggesting the stability of our meta-analysis (Fig. 5).
Moreover, we further investigated the significant associations ($P < 0.05$) observed in the present meta-analysis using the FPRP test. As listed in Table 4, the FPRP test results revealed that all 4 gene models (AA + AG vs. GG, AA vs. GG, AG vs. GG, A vs. G) of the SDF-1 rs1801157 gene polymorphism were truly associated with cancer risk ($FPRP = 0.011, 0.001, 0.008, 0.017$, respectively) at an $a$ priori probability level of $0.001$ with an OR of 1.5, especially in Asians. In addition, according to the results of the FPRP test, we confirmed that the SDF-1 rs1801157 gene polymorphism was only associated with lung cancer risk in the allele model (A vs. G, $FPRP = 0.019$), whereas the polymorphism was associated with susceptibility to urologic cancer in the dominant gene model (AA + AG vs. GG, $FPRP = 0.001$) at an $a$ priori probability level of $0.001$ and an OR of 1.5.

**Discussion**

Cancer has high morbidity and mortality worldwide. Previous studies have suggested that cancer risk factors include an unhealthy life style, environmental pollution, radiation, infection, and immunity dysfunction$^{48–47}$. Additionally, studies have increasingly focused on genetic factors$^{48–50}$. In recent years, numerous studies reported an association between the SDF-1 rs1801157 polymorphism and cancer susceptibility, but the results were inconsistent or inconclusive. In addition, a single study may lack sufficient power to detect the potentially small effect of the SDF-1 rs1801157 polymorphism on cancer, especially when the sample size is relatively small. Meta-analysis

**Table 1. Characteristics of case-control studies included in the meta-analysis.** BC = breast cancer; EC = endometrial cancer; RC = renal cancer; ALL = acute lymphatic leukaemia; CML = chronic myeloid leukaemia; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; CRC = colorectal cancer; GC = gastric cancer; PC = prostate cancer; HC = head cancer; NC = neck cancer; LAC = laryngeal cancer; BLC = bladder cancer; LC = lung cancer; CC = cervical cancer; MM = multiple myeloma; CLL = chronic lymphocytic leukaemia; OC = ovarian cancer; IGGMP = Illumina Golden Gate multiplex platform; PCR-RFLP = polymerase chain reaction-restricted fragment length polymorphism; DHPLC = denaturing high performance liquid chromatography.

**FPRP test results.** Moreover, we further investigated the significant associations ($P < 0.05$) observed in the present meta-analysis using the FPRP test. As listed in Table 4, the FPRP test results revealed that all 4 gene models (AA + AG vs. GG, AA vs. GG, AG vs. GG, A vs. G) of the SDF-1 rs1801157 gene polymorphism were truly associated with cancer risk (FPRP = 0.011, 0.001, 0.008, 0.017, respectively) at an $a$ priori probability level of 0.001 with an OR of 1.5, especially in Asians. In addition, according to the results of the FPRP test, we confirmed that the SDF-1 rs1801157 gene polymorphism was only associated with lung cancer risk in the allele model (A vs. G, FPRP = 0.019), whereas the polymorphism was associated with susceptibility to urologic cancer in the dominant gene model (AA + AG vs. GG, FPRP = 0.001) at an $a$ priori probability level of 0.001 and an OR of 1.5.

**Discussion**

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is a useful method for investigating cancer associations with genetic factors because this method uses a quantitative approach by combining the results of different studies on the same topic, potentially providing more reliable conclusions. Thus, we conducted a pooled analysis to investigate the association of the SDF-1 rs1801157 polymorphism and risk of cancer.

In fact, two recently published meta-analyses investigated the association between the SDF-1 rs1801157 gene polymorphism and cancer risk. One study included 29 papers involving 4932 cases and 7917 controls, and another article only included 4,435 cancer cases and 6,898 controls from 25 studies. Additionally, the two meta-analyses did not assess the quality of the included studies. Furthermore, the previous two studies did not use the FPRP test to explore truly significant associations, and the results of those studies were potentially unable to reflect the true association between the SDF-1 rs1801157 gene polymorphism and cancer risk. Therefore, we performed a meta-analysis and FPRP test to assess the association between the SDF-1 rs1801157 gene polymorphism and cancer risk.

In total, 8,062 cases and 9,814 controls were included in the current meta-analysis. Based on our overall meta-analysis and FPRP tests, we found that the SDF-1 rs1801157 polymorphism obviously increased the risk of cancer. Additionally, we identified significant heterogeneity between studies in the present meta-analysis. Although heterogeneity can be considered using the random-effect model, heterogeneity increases the probability of type-I errors. The following factors may have contributed to the significant heterogeneity: 1) different demographic and genetic characteristics of Caucasian, Asian and mixed populations; 2) different types of cancer may be caused by different mechanisms; 3) different stages of cancer in each study among the studied cancer patients; 4) different genotyping methods of each study; and 5) different qualities among included studies.

| First author | Year | Case | Control |
|--------------|------|------|---------|
| Bodelon C    | 2013 | 29   | 35     |
| Bracci FM    | 2010 | 6    | 14     |
| Cacina C     | 2012 | 12   | 6      |
| Cai C        | 2013 | 61   | 29     |
| de Lourdes Perim A | 2013 | 3   | 1     |
| de Oliveira CE | 2007 | 4    | 1      |
| de Oliveira KB | 2009 | 3   | 4     |
| de Oliveira KB | 2010 | 5   | 5     |
| Dumbir J     | 2007 | 5    | 4     |
| Gawron AJ    | 2011 | 9    | 25     |
| Hidalgo-Pascual M | 2007 | 909 | 25    |
| Hirata H     | 2007 | 17   | 13    |
| Isman FK     | 2012 | 17   | 22    |
| Khedimi B    | 2008 | 8    | 20    |
| Kontogianni P | 2013 | 29   | 35    |
| Kruszyna L   | 2010 | 9    | 5     |
| Kruszyna L   | 2010 | 3    | 2     |
| Kucukergin C | 2012 | 26   | 23    |
| Lee YL       | 2011 | 36   | 21    |
| Liarmakopoulos E | 2013 | 6   | 46    |
| Lin GT       | 2009 | 16   | 21    |
| Maley SN     | 2009 | 30   | 23    |
| Mazur G      | 2013 | 1    | 1     |
| Pemberton NC | 2008 | 114  | 170   |
| Petersen DC  | 2008 | NA   | NA    |
| Razmkhah M  | 2013 | 18   | 8     |
| Razmkhah M  | 2005 | 34   | 13    |
| Razmkhah M  | 2005 | 9    | 20    |
| Shi MD       | 2013 | 4    | 0     |
| Singh V      | 2014 | 9    | 0     |
| Tee YT       | 2012 | 16   | 11    |
| Vairaktaris E | 2008 | 4  | 5     |
| Vázquez-Lavista LG | 2009 | 3  | 3     |
| Wong HL      | 2010 | 7    | 13    |

Table 2. Distributions of the SDF-1 rs1801157 allele and genotypes in cases and controls. NA = not available.
Hence, to identify the cause of heterogeneity, we conducted subgroup analyses based on ethnicity and cancer type. The results suggested that the SDF-1 rs1801157 gene polymorphism strongly increased the cancer risk among Asians, whereas the heterozygote genotype (AG) of the SDF-1 rs1801157 gene polymorphism only weakly increased cancer susceptibility in Caucasians. Unfortunately, the SDF-1 rs1801157 gene polymorphism did not increase or decrease the cancer risk among mixed populations. Furthermore, the results of sub-group analyses after stratification based on cancer type indicated that the SDF-1 rs1801157 polymorphism increased the risk of breast cancer, urologic cancer, lung cancer, head and neck cancer, and haematological malignancies. However, the SDF-1 rs1801157 polymorphism did not influence gynaecological cancer and digestive system cancer susceptibility. Despite the fact that the heterogeneity was still detected when we performed stratified analyses based on ethnicity and cancer type, the subgroup analyses may provide more precise results compared with the overall analysis.

Several previous studies indicated that the published "statistically significant" results for genetic variants were false-positive findings, even in large and well-designed studies. Fortunately, we could use the FPRP test to estimate true significant associations in the current meta-analysis. The FPRP is calculated from the statistical power of the test, the observed p-value, and a given a priori probability for the association. Therefore, based on the positive results of the current meta-analysis, we further investigated whether a significant association between the SDF-1 rs1801157 gene polymorphism and cancer risk is "noteworthy". Interestingly, the FPRP test results revealed that the SDF-1 rs1801157 gene polymorphism actually increased cancer susceptibility. Additionally, the FPRP test also demonstrated that the SDF-1 rs1801157 gene polymorphism could increase cancer risk among Asians, but it did not increase cancer risk in Caucasians. Moreover, the results of the FPRP test confirmed that the SDF-1 rs1801157 gene polymorphism increased the risk of lung cancer and urologic cancer. Surprisingly, the significant associations with breast cancer, head and neck cancer, and haematological malignancies in the present meta-analysis were false positive at the a priori probability level of 0.001 and an OR of 1.5. Some of the discoveries may be false-positive findings due to the limited sample size in each stratum, so it is important to perform FPRP analysis to avoid these findings, especially when the sample size is not of sufficient size.

The mechanism by which the SDF-1 rs1801157 polymorphism affects cancer risk is unclear. Previous studies indicated that SDF-1 is a chemokine that plays a pivotal role in different stages of cancer development and metastasis. Combined with previous results and our present meta-analysis results, we put forward a simple
hypothesis that the SDF-1 rs1801157 polymorphism, which has a G > A transition in the 3′-UTR, may have an important regulatory function of up-regulating SDF-1 production and the high serum concentrations of SDF-1 might contribute to cancer susceptibility. Finally, people who carried the variant A allele are more likely to develop cancer, especially urologic cancer and lung cancer.

Several limitations in the present meta-analysis should be noted. First, the published studies include small sample sizes, and only published articles were included in a few databases. Thus, these limitations might lead to additional biases or overall overestimated associations. Moreover, a language bias potentially also occurred because the including articles were only published in English and Chinese. Second, given the lack sufficient data for each included study, we failed to perform further subgroup analysis to investigate the risk factors of cancer, such as gender, gene-environment/gene-gene interactions, life style and age. Third, a small number of studies were included in the subgroup analysis to investigate the association between the SDF-1 rs1801157 polymorphism and head and neck cancer risk, so we must be cautious when referring to the pooled results. A study with larger samples is needed to confirm the results in the future. Despite these limitations, we minimized the likelihood of bias throughout the entire process by creating a detailed protocol and carefully performing study identification, statistical analysis and data selection. Thus, the reliability of the results is guaranteed.

In conclusion, the current study suggested that the SDF-1 rs1801157 polymorphism may contribute to the risk of cancer in Asians. In particular, the polymorphism could increase urologic and lung cancer susceptibility. More well-designed studies with larger sample sizes focusing on ethnicities or cancer types should be conducted to confirm the results in the future.

Methods

Study selection. A systematic literature search of the PubMed, Embase, and Wanfang databases and the China National Knowledge Internet (CNKI) was performed to identify studies involving the relationship between the SDF-1 rs1801157 gene polymorphism and cancer susceptibility, with the last updated search being conducted on May 14, 2015. The following key words were used: (stromal cell derived factor-1 OR SDF-1 OR CXC chemokine ligand 12 OR CXCL12) AND (cancer OR tumour OR neoplasm OR malignancy OR leukaemia OR myeloma OR sarcoma OR lymphoma) AND (polymorphism OR mutation OR variant). The language was restricted to English and Chinese.
Inclusion and exclusive criteria. The inclusion criteria were defined as follows: 1) the study should be a case-control study; 2) the association between the SDF-1 rs1801157 polymorphism and cancer risk should be evaluated; 3) the available genotype or allele frequencies for counting the odds ratio (OR) and 95% confidence interval (CI) should be provided in the study; 4) the study should evaluate humans; and 5) the genotype distributions of control cohorts should be in Hardy-Weinberg equilibrium (HWE). The following exclusive criteria were adopted: 1) the study was not designed as a case-control study; 2) review, abstract or overlapping study; and 3) the study cannot provide available genotype or allele frequencies for determining the effect size.

Quality score evaluation. The qualities of included studies were assessed by the Newcastle-Ottawa Scale (case control study). The scale estimates quality based on three aspects: selection, comparability and exposure in the study. The total score ranged from 0 to 9, and a score greater than 6 was considered to represent high quality. In addition, we assessed the quality of the studies in a consensus meeting with all authors.

Data extraction. The independent authors (Xiang Tong and Huajiang Deng) collected detailed data from each study according to the inclusive criteria. If a disagreement was encountered, the third author (Xixi Wang) evaluated the articles. For each study, the first author, publication year, country, ethnicity, number of case and control groups, type of cancer, genotype and allele distribution, and genotyping method were extracted. The information is listed in Tables 1 and 2.

Statistical methods. The OR and 95% CI were used to estimate the effect strength of association between the SDF-1 rs1801157 polymorphism and cancer susceptibility. We calculated heterogeneity using the $\chi^2$-based Q-test and I-squared ($I^2$) statistics tests. The pooled OR was assessed by the random-effect model when the heterogeneity was considered to be statistically significant ($I^2 > 50\%$ and $P < 0.10$); alternatively, the fixed-effect model was applied. We explored the association between the SDF-1 rs1801157 polymorphism and cancer risk in

| Variables               | AA + AG vs. GG | AA vs. AG + GG | AA vs. GG | AG vs. GG | A vs. G |
|-------------------------|----------------|---------------|-----------|-----------|---------|
|                         | OR  | 95% CI | P   | OR  | 95% CI | P   | OR  | 95% CI | P   | OR  | 95% CI | P   |
| Total                   | 1.33 | 1.17–1.51 | <0.001 | 1.28 | 1.11–1.47 | 0.001 | 1.43 | 1.24–1.65 | <0.001 | 1.35 | 1.19–1.54 | <0.001 | 1.26 | 1.14–1.40 | <0.001 |
| Ethnicities             |     |         |      |     |         |      |     |         |      |     |         |      |     |         |      |
| Caucasian               | 1.07 | 0.98–1.16 | 0.15  | 1.03 | 0.82–1.29 | 0.81  | 1.07 | 0.85–1.35 | 0.55  | 1.10 | 1.00–1.21 | 0.05  | 1.07 | 1.00–1.15 | 0.06  |
| Asian                   | 1.63 | 1.34–1.98 | <0.001 | 1.42 | 1.05–1.93 | 0.02  | 1.71 | 1.28–2.30 | <0.001 | 1.58 | 1.28–1.95 | <0.001 | 1.45 | 1.25–1.68 | <0.001 |
| Mixed                   | 1.21 | 0.87–1.69 | 0.26  | 0.92 | 0.25–3.34 | 0.90  | 0.82 | 0.37–1.81 | 0.62  | 1.28 | 0.90–1.82 | 0.16  | 1.11 | 0.83–1.47 | 0.48  |
| Types                   |     |         |      |     |         |      |     |         |      |     |         |      |     |         |      |
| Breast cancer           | 1.26 | 1.11–1.44 | <0.001 | 1.21 | 0.93–1.59 | 0.16  | 1.36 | 1.03–1.79 | 0.03  | 1.26 | 1.10–1.44 | <0.001 | 1.20 | 1.08–1.33 | <0.001 |
| Gynecological cancer    | 0.98 | 0.83–1.16 | 0.81  | 1.36 | 0.93–1.99 | 0.12  | 1.36 | 0.92–2.01 | 0.13  | 0.94 | 0.79–1.22 | 0.52  | 1.03 | 0.89–1.18 | 0.71  |
| Urologic cancer         | 1.56 | 1.32–1.85 | <0.001 | 1.34 | 0.75–2.38 | 0.32  | 1.62 | 0.97–2.69 | 0.06  | 1.46 | 1.10–1.93 | <0.001 | 1.31 | 1.09–1.57 | <0.001 |
| Digestive system cancer | 1.25 | 0.79–1.98 | 0.34  | 0.83 | 0.55–1.27 | 0.40  | 0.88 | 0.57–1.35 | 0.55  | 1.38 | 0.82–2.33 | 0.23  | 1.26 | 0.80–1.97 | 0.32  |
| Hematologic malignancy  | 1.17 | 0.97–1.41 | 0.09  | 0.95 | 0.57–1.59 | 0.98  | 1.06 | 0.63–1.78 | 0.83  | 1.29 | 1.04–1.59 | 0.02  | 1.18 | 0.99–1.40 | 0.07  |
| Lung cancer             | 1.80 | 1.36–2.39 | <0.001 | 2.24 | 1.41–3.57 | <0.001 | 2.86 | 1.75–4.69 | <0.001 | 1.62 | 1.20–2.18 | <0.001 | 1.65 | 1.34–2.04 | <0.001 |
| Head and neck cancer    | 1.3  | 0.68–2.48 | 0.43  | 0.76 | 0.40–1.46 | 0.41  | 0.92 | 0.47–1.80 | 0.81  | 1.35 | 0.70–2.61 | 0.37  | 1.16 | 0.71–1.91 | 0.55  |

Table 3. Summary the results of the total and subgroup analyses in different genetic models. OR = odds ratio; CI = confidence interval.

Figure 4. Funnel plot of the association between the SDF-1 rs1801157 polymorphism and cancer risk.
Figure 5. Sensitivity analysis of the association between the SDF-1 rs1801157 polymorphism and cancer risk.

| Gene models | OR (95% CI) | Power  | Prior Probability =0.001 |
|-------------|-------------|--------|-------------------------|
| **AA + AG vs. GG** |             |        |                         |
| Total       | 1.33 (1.17–1.51) | 0.968  | 0.011                   |
| Asians      | 1.63 (1.34–1.98) | 0.201  | 0.004                   |
| Breast cancer | 1.26 (1.11–1.44) | 0.995  | 0.41                    |
| Urologic cancer | 1.56 (1.32–1.85) | 0.326  | 0.001                   |
| Lung cancer | 1.80 (1.36–2.39) | 0.104  | 0.318                   |
| **AA vs. AG + GG** |             |        |                         |
| Total       | 1.28 (1.11–1.47) | 0.988  | 0.323                   |
| Asian       | 1.42 (1.05–1.93) | 0.637  | 0.975                   |
| Lung cancer | 2.24 (1.41–3.57) | 0.046  | 0.938                   |
| **AA vs. GG** |             |        |                         |
| Total       | 1.43 (1.24–1.65) | 0.744  | 0.001                   |
| Asians      | 1.71 (1.28–2.30) | 0.193  | 0.668                   |
| Breast cancer | 1.36 (1.03–1.79) | 0.758  | 0.974                   |
| Lung cancer | 2.86 (1.75–4.69) | 0.005  | 0.856                   |
| **AG vs. GG** |             |        |                         |
| Total       | 1.35 (1.19–1.54) | 0.942  | 0.008                   |
| Caucasians | 1.10 (1.00–1.21) | 1      | 0.980                   |
| Asians      | 1.58 (1.28–1.95) | 0.314  | 0.061                   |
| Breast cancer | 1.26 (1.10–1.44) | 0.995  | 0.410                   |
| Urologic cancer | 1.46 (1.10–1.93) | 0.575  | 0.932                   |
| Hematologic malignancy | 1.29 (1.04–1.59) | 0.921  | 0.949                   |
| Lung cancer | 1.62 (1.20–2.18) | 0.306  | 0.826                   |
| **A vs. G** |             |        |                         |
| Total       | 1.26 (1.14–1.40) | 0.999  | 0.017                   |
| Asians      | 1.45 (1.25–1.68) | 0.674  | 0.001                   |
| Breast cancer | 1.20 (1.08–1.33) | 1      | 0.339                   |
| Urologic cancer | 1.31 (1.09–1.57) | 0.929  | 0.788                   |
| Lung cancer | 1.65 (1.34–2.04) | 0.189  | 0.019                   |

Table 4. The results of the FPRP tests in each gene models. OR = odds ratio; FPRP = false positive report probability.
different gene models (AA + AG vs. GG, AA vs. AG + GG, AA vs. GG, AG vs. GG and A vs. G). To evaluate the effects of ethnicity and type of cancer, we also performed subgroup analyses based on ethnicity group and type of cancer.

In addition, to evaluate whether significant associations (P < 0.05) detected in the present study are “note-worthy”, we further calculated the FPRP value at a probability level of 0.001 and an OR of 1.5 58. As suggested by the previous study59, we set a FPRP cut-off value of 0.2, and only FPRP results < 0.2 were considered to be “note-worthy”. Publication bias was assessed by several methods. A visual inspection of asymmetry in funnel plots was performed. Furthermore, the Begger’s and Egger’s tests were used to assess the publication bias60. Additionally, HWE was assessed in each study using the Chi-square before the present meta-analysis was performed. All analyses were conducted using STATA 11.0 software.

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