The association between XRCC3 rs1799794 polymorphism and cancer risk: a meta-analysis of 34 case-control studies

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Abstract

Background: Studies on the XRCC3 rs1799794 polymorphism show that this polymorphism is involved in a variety of cancers, but its specific relationships or effects are not consistent. The purpose of this meta-analysis was to investigate the association between rs1799794 polymorphism and susceptibility to cancer.

Methods: PubMed, Embase, the Cochrane Library, Web of Science, and Scopus were searched for eligible studies through June 11, 2019. All analyses were performed with Stata 14.0. Subgroup analyses were performed by cancer type, ethnicity, source of control, and detection method. A total of 37 studies with 23,537 cases and 30,649 controls were included in this meta-analysis.

Results: XRCC3 rs1799794 increased cancer risk in the dominant model and heterozygous model (GG+AG vs. AA: odds ratio [OR] = 1.04, 95% confidence interval [CI] = 1.00–1.08, P = 0.051; AG vs. AA: OR = 1.05, 95% CI = 1.00–1.01, P = 0.015). The existence of rs1799794 increased the risk of breast cancer and thyroid cancer, but reduced the risk of ovarian cancer. In addition, rs1799794 increased the risk of cancer in the Caucasian population.

Conclusion: This meta-analysis confirms that XRCC3 rs1799794 is related to cancer risk, especially increased risk for breast cancer and thyroid cancer and reduced risk for ovarian cancer. However, well-designed large-scale studies are required to further evaluate the results.

Background

Cancer is the leading cause of death worldwide, and the number of patients with cancer is increasing [1]. The occurrence of cancer is related to many factors, including environmental, lifestyle, genetic and other factors. Among them, gene mutation is a kind of genetic factor, which has a great influence on cancer risk [2]. The mutation in BRCA1 and BRCA2 is related to the increase risk of breast cancer [3]. XPF rs2276466 polymorphism is related to neurogenic cancer [4].

X-ray repair cross-complementing group 3 (XRCC3), functions in the homologous recombination (HR) repair of DNA crosslinks [5] and double-strand breaks [6]. Based on the function of XRCC3, XRCC3 gene mutations are related to the occurrence and development of many diseases. For example, XRCC3 241Thr/Met genotype promotes left ventricular hypertrophy by inhibiting DNA damage repair [7]. Mutations in the XRCC3 gene affect mitochondrial DNA integrity [8]. XRCC3 rs861539 polymorphism is associated with poor prognosis of breast cancer patients [9]. The mutation sites that have been studied more about the relationship between XRCC3 gene and cancer are rs861539, rs1799794 and rs1799796 [10]. However, results remain fairly conflicting rather than conclusive. A number of meta-analyses have investigated the relationship between rs861539 and susceptibility to various cancers [11-33]. However, there have been few meta-studies on rs1799794 and susceptibility to cancer [28, 30, 31, 33, 34]. Therefore, we conducted this meta-analysis to analyze the relationship between rs1799794 and susceptibility to cancer on the basis of more data.

Methods

Search strategies

We comprehensively searched five databases (PubMed, Embase, the Cochrane Library, Web of Science, and Scopus) for research published as of June 11, 2019, using relevant MeSH terms and entry terms. The keywords of XRCC3 included X-ray repair cross complementing 3, rs1799794, 4541A/G, XRCC3. The MeSH term and entry terms of polymorphism were genetic polymorphism [MeSH terms]; polymorphisms, genetic; genetic polymorphisms; genetic polymorphism; polymorphism (genetics); polymorphisms (genetics); polymorphism, single nucleotide; nucleotide polymorphism, single; nucleotide polymorphisms, single; polymorphisms, single nucleotide; single nucleotide polymorphisms; polymorphisms; polymorphism; variant; mutation; single nucleotide polymorphism; SNP. The MeSH term and entry terms of cancer were neoplasm [MeSH terms], neoplasms, neoplasia, neoplasias, neoplasm, tumors, tumor, cancer, cancers, carcinoma, carcinogenesis, tumour. Furthermore, we refined the search results of related studies by looking at the list of references included in each article.

Selection criteria

Relevant studies were included in accordance with the inclusion criteria and exclusion criteria, which were similar to those described in the previous study (PMID: 30867406). Original case-control study focused on the relationship between rs1799794 and cancer risk with the frequency of XRCC3 rs1799794 mutant genotypes were included. While conference abstracts or reports, reviews or meta-analyses, republished articles, and studies with insufficient data were excluded.

Data extraction and quality assessment

The following data from each selected article were collected: the surname of the first author, the publication year, country, ethnicity, cancer types, and methods of genotyping XRCC3 rs1799794 polymorphism. The quality of eligible case-control studies was estimated using the Newcastle-Ottawa Scale [35].

Statistical analysis

The relationship between XRCC3 rs1799794 polymorphisms and cancer risk were evaluated using odds ratios (ORs) and 95% confidence intervals (CI) under five genetic models (G vs. A, GG vs. AA, GG+GA vs. AA, GG vs. GA+AA, GA vs. AA) as previous study. If P < 0.05 or the 95% CI did not include 1, the result was considered statistically significant. Cochran’s Q with chi-square (with P<0.1 or I² > 25% indicated significant heterogeneity [36-38], we analyzed the data using a random effects model [39]. If the opposite held,
a fixed effects model was chosen. We also performed subgroup analyses and a sensitivity analysis to explore sources of heterogeneity. Subgroup analyses stratified studies by cancer type (ovarian cancer, acute lymphoblastic leukemia, breast cancer, thyroid cancer, bladder cancer, lung cancer, other), ethnicity (Arabian, Asian, Caucasian, mixed), sample size (<100, >100), the publication year (≤2010, >2010), detection method (PCR-RFLP, sequencing, TaqMan, PCR, ND, other), and source of control (HB, PB, mixed, nested). We assessed publication bias using funnel plots and Egger's test (P < 0.05). Statistical calculations were performed with Stata 14.0.

Results

Literature search and study characteristics

Finally, 3,467 potentially relevant published works were identified (997 in PubMed, 27 in the Cochrane library, 855 in Embase, 696 in Scopus, and 889 in Web of Science). Of these, duplicates (1,959) and works not related to cancer and rs1799794 polymorphism (1,451) were excluded. Then 23 of these studies were excluded after reviewing full texts. The remaining 37 works (43 studies) were included in this meta-analysis [40-76]. Because two studies in Auranen et al. (2005) were duplicated in Quaye et al. (2009), we only extracted data from these studies from Auranen et al. (2005) to avoid duplication; thus, one article included four studies [66], and there were included two studies each [68, 70, 71]. The flow chart of the literature selection process is shown in Figure 1.

There were a total of 23,537 cases and 30,649 controls in these 37 works, and 3 were conducted among Arabians [40, 48, 55], 14 among Asians [41, 42, 45-47, 49, 50, 53, 54, 56, 58, 59, 66, 67], and 24 among Caucasians [43, 44, 51, 52, 57, 60-62, 64, 66, 69-76]; 2 were conducted among mixed populations [63, 65]. In addition, in terms of cancer type, ovarian cancer (n = 4) [40, 62, 70], acute lymphoblastic leukemia (n = 3) [41, 52, 57], breast cancer (n = 13) [44, 48, 49, 55, 61, 66, 68, 73, 75], thyroid cancer (n = 4) [42, 46, 47, 67], bladder cancer (n = 4) [45, 63, 65, 69], lung cancer (n = 3) [53, 59, 72], and other cancer (hepatocellular carcinoma, leiomyoma, nasopharyngeal carcinoma, osteosarcoma, oral cancer, glioma, head and neck cancer, myeloma, endometrial cancer, colorectal adenoma, melanoma skin cancer) [43, 50, 51, 54, 56, 58, 60, 64, 71, 74, 76] were studied. The basic information of each study is presented in Table 1. And we took sensitivity analysis for studies that do not conform to HWE.

Meta-analysis and subgroup analyses

The value of $I^2$ in the five genetic models was greater than 25%, and $P_2 < 0.10$, so pooled ORs for the five genetic models were calculated with a random effects model. There was no obvious correlation between rs1799794 and cancer risk ($P_2 > 0.05$; Table 2).

Subgroup analyses were then performed based on cancer type, ethnicity, detection method, the publication year, source of control, and sample size to investigate sources of heterogeneity (Table 3). In the subgroup analysis based on cancer type, a significantly increased risk for thyroid cancer was observed in the five models (G vs. A: OR = 1.27, 95% CI = 1.01–1.61, $I^2 = 71.2%$; GG+AG vs. AA: OR = 1.36, 95% CI = 1.15–1.61, $I^2 = 55.4%$; GG vs. AA+AG: OR = 1.38, 95% CI = 1.09–1.75, $I^2 = 29.8%$; GG vs. AA: OR = 1.50, 95% CI = 1.17–1.93, $I^2 = 45.7%$; AG vs. AA: OR = 1.27, 95% CI = 1.05–1.53, $I^2 = 33.2%$), a significantly increased risk for breast cancer was found in the heterozygous model (OR = 1.08, 95% CI = 1.02–1.13, $I^2 = 42.3%$), and a decreased risk for ovarian cancer was found in the recessive model and homozygous model (GG vs. AA+AG: OR = 0.69, 95% CI = 0.51–0.93, $I^2 = 0.0%$; GG vs. AA: OR = 0.71, 95% CI = 0.53–0.96, $I^2 = 0.0%$).

In the subgroup analysis based on ethnicity, rs1799794 was associated with increased cancer risk in the Caucasian population according to the heterozygous model (AG vs. AA: OR = 1.05, 95% CI = 1.01–1.10, $I^2 = 0.0%$). In the subgroup analysis based on source of control, we found a significantly increased risk for PB (population based) in the dominant model and heterozygous model (GG+AG vs. AA: OR = 1.06, 95% CI = 1.01–1.12, $I^2 = 0.0%$; AG vs. AA: OR = 1.09, 95% CI = 1.03–1.15, $I^2 = 0.0%$). In the subgroup analysis based on detection method, sequencing was associated with a significantly increased cancer risk in the allele model, dominant model, and heterozygous model (G vs. A: OR = 2.60, 95% CI = 1.37–4.94, $I^2 = 0.0%$; GG+AG vs. AA: OR = 4.00, 95% CI = 1.82–8.80, $I^2 = 0.0%$; AG vs. AA: OR = 4.00, 95% CI = 1.79–8.94, $I^2 = 0.0%$). In the subgroup analysis based on sample size, AG carriers were 2.82 times more likely to develop cancer than AA carriers (95% CI = 1.42–5.57, $P_2 = 0.003$). In the subgroup analysis based on the publication year, studies published before 2010 showed that AG carriers were 1.05 times more likely to develop cancer than AA carriers (95% CI = 1.00–1.10, $P_2 = 0.047$).

Publication bias

The shape of the funnel plots (Figure 2) and Egger's test (allele: $P = 0.108$, dominant: $P = 0.177$, recessive: $P = 0.240$, homozygous: $P = 0.132$, heterozygous: $P = 0.177$) showed no publication bias.

Sensitivity analysis

Eight studies [41, 42, 48-50, 53, 54, 56] had $P_{HWE} < 0.05$, but for two studies [51, 63] $P_{HWE}$ was not available. We compared the combined results before and after excluding these 10 studies and there were slight changes in the results. When the subgroup analysis was performed according to cancer type, there were no significant associations between rs1799794 polymorphism and increased risk for thyroid cancer in the recessive model, homozygous model, or heterozygous model (GG vs. AA+AG: OR = 1.16, 95% CI = 0.87–1.55, $I^2 = 0.0%$; GG vs. AA: OR = 1.24, 95% CI = 0.90–1.69, $I^2 = 0.0%$; AG vs. AA: OR = 1.22, 95% CI = 0.98–1.51, $I^2 = 49.4%$); and rs3116496 was related to a decreased risk for lung cancer in the five models (A vs. G: OR = 0.80, 95% CI = 0.70–0.92, $I^2 = 18.1%$; GG+AG vs. AA: OR = 0.76, 95% CI = 0.62–0.93, $I^2 = 4.9%$; GG vs. AA+AG: OR = 0.75, 95% CI = 0.59–0.96, $I^2 = 0.0%$; GG vs. AA: OR = 0.65, 95% CI = 0.49–0.87, $I^2 = 0.0%$; AG vs. AA: OR = 0.80, 95% CI = 0.64–0.99, $I^2 = 0.0%$); no changes were observed for the other cancers. No significant changes were found in the subgroup analyses by ethnicity and source of control.

Discussion

Finally, 3,467 potentially relevant published works were identified (997 in PubMed, 27 in the Cochrane library, 855 in Embase, 696 in Scopus, and 889 in Web of Science). Of these, duplicates (1,959) and works not related to cancer and rs1799794 polymorphism (1,451) were excluded. Then 23 of these studies were excluded after reviewing full texts. The remaining 37 works (43 studies) were included in this meta-analysis [40-76]. Because two studies in Auranen et al. (2005) were duplicated in Quaye et al. (2009), we only extracted data from these studies from Auranen et al. (2005) to avoid duplication; thus, one article included four studies [66], and there were included two studies each [68, 70, 71]. The flow chart of the literature selection process is shown in Figure 1.
Our study shows that XRCC3 rs1799794 is irrelevant to cancer risk. In addition, the risk for thyroid cancer and breast cancer increase significantly in patients with rs1799794, and Caucasian populations are more likely to develop these cancers while having a decreased risk for ovarian cancer. We excluded articles that did not conform to HWE and reanalyzed the data. Compared to the previous results, rs3116496 was related to a decreased risk for lung cancer in the five models, although the other results were not much changed (data not shown).

Moderate heterogeneity was found in this meta-analysis. First, we used random models when significant heterogeneity. Second, we performed subgroup analyses to explore sources of heterogeneity. As shown in Table 3, in the subgroup analysis based on ethnicity, heterogeneity increased in Arabian/Asian populations but was 0% in Caucasian populations, which suggests that ethnicity may be a factor in heterogeneity. Furthermore, we analyzed studies stratified by cancer type, detection method, source of control, and sample size. Ethnicity, cancer type, source of control, and sample size may be the source of inter-research heterogeneity. In addition, a sensitivity analysis suggested that the current findings were reliable.

To date, five meta-analyses of the impact of rs1799794 on cancer risk have been performed [28, 30, 31, 33, 34] on rs1799794 and susceptibility to pan-cancer [28], breast cancer [30, 34], bladder cancer [33], and ovarian cancer [31]. To the best of our knowledge, ours is currently the most comprehensive meta-analysis of correlations between rs1799794 polymorphisms and cancer. There are many differences between the results of this study and previous studies. According to Qiu et al.’s research on rs1799794 and susceptibility to breast cancer, which included four studies in three papers, rs1799794 was associated with a statistically significant increase in cancer risk in the dominant model (GG+AG vs. AA: OR = 1.09, 95% CI = 1.01–1.17, P_H = 0.15), whereas our results showed an increased risk for breast cancer in AG carriers, different from the protective effect found previously [48]. In addition, our study found that the G allele might be a dominant gene and found an increased risk for thyroid cancer.

Our study included a large number of samples and conducted a stratified analysis, which played an important role in the reliability of the research results. At the same time, there are problems that cannot be ignored: the presence of heterogeneity that may due to ethnicity, source of control, status, or cancer type; the lack of relevant data published in other languages and evaluation of the interaction between cancer-related factors.

**Conclusion**

In conclusion, this meta-analysis found no association between XRCC3 rs1799794 and cancer risk, but XRCC3 rs1799794 was associated with breast cancer and thyroid cancer as well as with Caucasian populations. In addition, detection method, source of control, and sample size played a role in heterogeneity and in the results. Well-designed large-scale studies are required to further evaluate the results.

**Abbreviations**

SNP: single nucleotide polymorphism; XRCC3: X-ray repair cross-complementing group 3; HR: homologous recombination; OR: odds ratio; CI: confidence interval.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

All data generated or analyzed during this study are included in this manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

WQL: Drafting of manuscript/Analysis and interpretation of data. SMM, LL, ZYK, HBZ: Acquisition of data/Analysis and interpretation of data/Critical revision. JY: Study conception and design/Analysis and interpretation of data/Critical revision. All authors have read and approved the final manuscript.

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Not applicable
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**Tables**

**Table 1** Characteristics of the individual studies included in the meta-analysis...
| Author            | Year  | Country                | Ethnicity | Cancer type                     | Genotyping method | Control | Cases/control | Cases | Control |
|-------------------|-------|------------------------|-----------|---------------------------------|-------------------|---------|----------------|-------|---------|
| Mackawy          | 2019  | Egypt                  | Arabian   | ovarian carcinoma               | PCR-RFLP          | HB      | 50/20          | 14    | 20      |
| Pei              | 2018  | China                  | Asian     | acute lymphoblastic leukemia    | PCR-RFLP          | PB      | 266/266        | 55    | 144     |
| Al Zoubi         | 2017  | Italy                  | Caucasian | breast cancer                   | Sequencing        | HB      | 23/16          | 8     | 14      |
| De Mattia        | 2017  | Italy                  | Caucasian | hepatocellular cancer           | TaqMan            | HB      | 192/192        | 128   | 52      |
| Sarwar           | 2017  | Pakistan               | Asian     | thyroid cancer                  | ARMS-PCR          | HB      | 456/400        | 289   | 90      |
| Yan              | 2016  | China                  | Asian     | thyroid carcinoma               | PCR               | HB      | 276/403        | 116   | 127     |
| Zhu              | 2016  | China                  | Asian     | bladder cancer                  | TaqMan            | HB      | 184/260        | 72    | 53      |
| Ali              | 2016  | Saudi Arabia           | Arabian   | breast cancer                   | PCR-RFLP          | HB      | 143/145        | 102   | 40      |
| Chang            | 2015  | China                  | Asian     | leiomyoma                       | PCR-RFLP          | HB      | 166/474        | 35    | 91      |
| Chen             | 2015  | China                  | Asian     | lung cancer                     | PCR-RFLP          | HB      | 358/716        | 70    | 202     |
| Liu              | 2015  | China                  | Asian     | nasopharyngeal carcinoma        | PCR-RFLP          | HB      | 176/880        | 33    | 99      |
| Su               | 2015  | China                  | Asian     | breast cancer                   | PCR-RFLP          | HB      | 1232/1232      | 239   | 696     |
| Al Zoubi         | 2015  | Jordan                 | Arabian   | breast cancer                   | Sequencing        | HB      | 46/31          | 16    | 28      |
| Yuan             | 2015  | China                  | Asian     | papillary thyroid cancer        | PCR               | HB      | 183/367        | 77    | 84      |
| Goričar          | 2015  | Slovenia               | Caucasian | acute lymphoblastic leukemia    | TaqMan            | PB      | 121/184        | 89    | 117     |
| Goričar          | 2015  | Slovenia               | Caucasian | osteosarcoma                    | TaqMan            | PB      | 79/373         | 47    | 247     |
| Smolkova         | 2014  | Germany                | Caucasian | acute lymphoblastic leukaemia   | TaqMan            | HB      | 460/547        | 286   | 155     |
| TSAI             | 2014  | China                  | Asian     | oral cancer                     | PCR-RFLP          | HB      | 788/956        | 155   | 438     |
| He               | 2013  | China                  | Asian     | lung cancer                     | PCR               | HB      | 507/661        | 180   | 230     |
| Zhao             | 2013  | China                  | Asian     | glioma                          | TaqMan            | HB      | 384/384        | 83    | 201     |
| Gresner          | 2012  | Poland                 | Caucasian | head and neck cancer            | PCR-RFLP          | PB      | 81/100         | 45    | 31      |
| VRAL             | 2011  | Belgium                | Caucasian | breast cancer                   | PCR-RFLP or SnapShot technique | HB      | 343/172        | 220   | 108     |
| Quaye            | 2009  | mixed                  | Caucasian | ovarian cancer                  | TaqMan            | PB      | 1461/2307      | 940   | 484     |
| Andrew           | 2009  | USA                    | Mixed     | bladder cancer                  | PCR-RFLP          | PB      | 342/559        | 190   | 333     |
| Hayden           | 2007  | Germany, Italy, Spain, Spain, Ireland, France, Czech Republic and the Irish | Caucasian | myeloma                         | TaqMan mixed      |        |                |       |         |
| Ni               | 2006  | China                  | Asian     | thyroid carcinoma               | PCR-RFLP          | HB      | 191/201        | 66    | 81      |
| Garcia-Closas    | 2006  | Poland                 | Caucasian | breast cancer                   | ND                | PB      | 1920/2218      | 1210  | 632     |
| Wu               | 2006  | USA                    | Mixed     | bladder cancer                  | PCR-RFLP          | HB      | 599/595        | 402   | 185     |
| Paul Pharoah     | 2006  | Thailand               | Asian     | breast cancer                   | ND                | PB      | 465/389        | 153   | 217     |
Table 2. The results of the meta-analyses under different genetic models for all studies

| Genetic model               | Number | \(I^2\)   | \(P_H\)   | OR (95% CI)        | \(P_Z\) |
|-----------------------------|--------|-----------|-----------|-------------------|---------|
| G VS A                      | 40     | 47.50%    | 0.001     | 1.02 (0.98-1.07)  | 0.377   |
| GG VS A                     | 40     | 30.20%    | 0.039     | 0.98 (0.89-1.08)  | 0.713   |
| GG + GA VS AA               | 43     | 40.0%     | 0.004     | 1.04 (0.98-1.09)  | 0.207   |
| GG VS GA + AA               | 40     | 34.10%    | 0.02      | 0.98 (0.90-1.07)  | 0.696   |
| GA VS AA                    | 40     | 39.40%    | 0.006     | 1.04 (0.99-1.11)  | 0.134   |

Table 3. Results of meta-analysis for polymorphisms in different subgroups and cancer susceptibility
| Comparison            | Subgroup        | Number | I²    | P_H | P_Z    | OR (95% CI)     |
|-----------------------|-----------------|--------|-------|-----|--------|-----------------|
| G VS A                | Ethnicity       |        |       |     |        |                 |
|                       | Arabian         | 3      | 84.9% | 0.001 | 0.752 | 0.86(0.33-2.23) |
|                       | Asian           | 14     | 64.8% | <0.001 | 0.255 | 1.05(0.96-1.15) |
|                       | Caucasian       | 22     | 0.0%  | 0.661 | 0.502 | 1.01(0.98-1.05) |
|                       | Mixed           | 1      | NA    | NA   | 0.940 | 0.99(0.80-1.23) |
|                       | Cancer type     |        |       |     |        |                 |
|                       | Ovarian cancer  | 4      | 0.0%  | 0.547 | 0.848 | 0.99(0.90-1.09) |
|                       | Acute lymphoblastic leukemia | 2 | 0.0% | 0.887 | 0.979 | 1.00(0.85-1.18) |
|                       | Breast cancer   | 13     | 58.6% | 0.004 | 0.494 | 1.03(0.95-1.10) |
|                       | Thyroid cancer  | 4      | 71.2% | 0.015 | 0.043 | 1.27(1.01-1.61) |
|                       | bladder cancer  | 3      | 0.0%  | 0.921 | 0.815 | 0.98(0.85-1.13) |
|                       | lung cancer     | 3      | 60.1% | 0.082 | 0.166 | 0.88(0.74-1.05) |
|                       | others          | 11     | 0.0%  | 0.902 | 0.822 | 1.01(0.91-1.08) |
|                       | Method          |        |       |     |        |                 |
|                       | PCR-RFLP        | 12     | 22.3% | 0.225 | 0.657 | 0.99(0.93-1.05) |
|                       | Sequencing      | 2      | 0.0%  | 0.828 | 0.004 | 2.60(1.37-4.94) |
|                       | TaqMan          | 13     | 0.0%  | 0.886 | 0.475 | 1.02(0.97-1.07) |
|                       | PCR             | 4      | 82.4% | 0.001 | 0.913 | 1.02(0.78-1.33) |
|                       | ND              | 6      | 14.6% | 0.321 | 0.663 | 1.01(0.96-1.06) |
|                       | others          | 3      | 68.3% | 0.043 | 0.089 | 1.32(0.96-1.82) |
|                       | Source of control|      |       |     |        |                 |
|                       | HB              | 23     | 66.0% | <0.001 | 0.445 | 1.03(0.95-1.13) |
|                       | PB              | 12     | 0.0%  | 0.892 | 0.135 | 1.03(0.99-1.08) |
|                       | Mixed           | 1      | NA    | NA   | 0.442 | 0.89(0.67-1.19) |
|                       | Nested          | 4      | 0.0%  | 0.874 | 0.294 | 0.95(0.86-1.05) |
|                       | Sample size     |        |       |     |        |                 |
|                       | < 100           | 3      | 77.1% | 0.013 | 0.419 | 1.54(0.54-4.43) |
|                       | > 100           | 37     | 43.7% | 0.003 | 0.424 | 1.02(0.98-1.07) |
|                       | Year            |        |       |     |        |                 |
|                       | ≤ 2010          | 20     | 0.0%  | 0.910 | 0.700 | 1.01(0.97-1.04) |
|                       | > 2010          | 20     | 69.5% | 0.000 | 0.272 | 1.06(0.96-1.17) |
|                       | GG+AG VS AA     | Ethnicity       |        |       |     |        |                 |
|                       | Arabian         | 3      | 79.8% | 0.007 | 0.739 | 1.21(0.39-3.76) |
|                       | Asian           | 14     | 64.4% | <0.001 | 0.547 | 1.04(0.91-1.20) |
|                       | Caucasian       | 24     | 0.6%  | 0.453 | 0.119 | 1.03(0.99-1.08) |
|                       | Mixed           | 2      | 0.0%  | 0.620 | 0.765 | 1.03(0.85-1.24) |
|                       | Cancer type     |        |       |     |        |                 |
|                       | Ovarian cancer  | 4      | 0.0%  | 0.887 | 0.439 | 1.05(0.93-1.17) |
|                       | Acute lymphoblastic leukemia | 3 | 24.4% | 0.267 | 0.397 | 0.90(0.75-1.12) |
|                       | Breast cancer   | 13     | 47.0% | 0.031 | 0.037 | 1.06(0.98-1.15) |
|                       | Thyroid cancer  | 4      | 55.4% | 0.081 | 0.033 | 1.36(1.15-1.61) |
|                       | bladder cancer  | 4      | 59.1% | 0.062 | 0.370 | 0.89(0.70-1.14) |
|                       | lung cancer     | 3      | 51.2% | 0.129 | 0.207 | 0.85(0.66-1.09) |
| Method           | Sample size | Year     | Ethnicity          | Cancer type                     |
|------------------|-------------|----------|--------------------|---------------------------------|
| PCR-RFLP         | 13          | 3        | Arabian            | Ovarian cancer                 |
|                  |             |          | Asian              | Acute lymphoblastic leukemia    |
|                  |             |          | Caucasian          | Breast cancer                   |
|                  |             |          | Mixed              | Thyroid cancer                  |
|                  |             |          |                   | bladder cancer                  |
|                  |             |          |                   | lung cancer                     |
| ND               | 6           | 3        | Arabian            | others                          |
| others           | 3           |          |                    |                                |
| Source of control|             |          | HB                 |                                |
|                  |             |          | PB                 |                                |
|                  |             |          | Mixed              |                                |
| Nested           | 4           |          |                    |                                |

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| Sample size   | < 100 | > 100 |
|--------------|-------|-------|
|              | 3     | 37    |
|              | 0.0%  | 36.9% |
|              | 0.537 | 0.014 |
|              | 0.339 | 0.766 |
|              | 0.64(0.26-1.59) | 0.99(0.90-1.07) |

| Year         | ≤ 2010 | > 2010 |
|--------------|--------|--------|
|              | 20     | 20     |
|              | 0.0%   | 58.0%  |
|              | 0.928  | 0.001  |
|              | 0.068  | 0.374  |
|              | 0.94(0.83-1.01) | 1.08(0.92-1.27) |

| GG VS AA     | Ethnicity          |
|--------------|--------------------|
|              | Arabian             |
|              | Asian               |
|              | Caucasian           |
|              | Mixed               |

| Cancer type  | Ovarian cancer | Acute lymphoblastic leukemia | Breast cancer | Thyroid cancer | bladder cancer | lung cancer | others |
|--------------|---------------|------------------------------|--------------|---------------|---------------|------------|--------|
|              | 4             | 2                            | 13           | 4             | 3             | 3          | 11     |
|              | 0.0%          | 0.0%                         | 37.7%        | 45.7%         | 0.0%          | 53.1%      | 0.0%   |
|              | 0.705         | 0.836                        | 0.082        | 0.137         | 0.860         | 0.119      | 0.0%   |
|              | 0.028         | 0.961                        | 0.311        | 0.001         | 0.773         | 0.019      | 0.798  |
|              | 0.71(0.53-0.96) | 0.99(0.67-1.47) | 0.94(0.85-1.05) | 1.50(1.17-1.93) | 1.06(0.72-1.55) | 0.79(0.56-1.11) | 1.02(0.88-1.19) |

| Method       | PCR-RFLP | Sequencing | TaqMan | PCR | ND | others |
|--------------|----------|------------|--------|-----|----|--------|
|              | 12       | 2          | 13     | 4   | 6  | 3      |
|              | 10.7%    | 0.0%       | 37.7%  | 73.8%| 2.7%| 0.0%   |
|              | 0.340    | 0.837      | 0.082  | 0.010| 0.399| 0.409  |
|              | 0.591    | 0.264      | 0.311  | 0.937| 0.436| P<0.001|
|              | 0.96(0.85-1.10) | 3.09(0.43-22.45) | 0.94(0.85-1.05) | 0.98(0.61-1.58) | 0.94(0.82-1.09) | 1.97(1.36-2.87) |

| Source of control | HB | PB | Mixed | Nested |
|-------------------|----|----|-------|--------|
|                   | 23 | 12 | 1     | 4      |
|                   | 52.8% | 0.0% | NA | 0.0% |
|                   | 0.002 | 0.911 | NA | 0.553 |
|                   | 0.628 | 0.185 | NA | 0.737 |
|                   | 1.04(0.88-1.24) | 0.92(0.82-1.04) | 0.81(0.36-1.80) | 0.96(0.76-1.21) |

| Sample size       | < 100 | > 100 |
|-------------------|-------|-------|
|                   | 3     | 37    |
|                   | 18.0% | 32.5 |
|                   | 0.295 | 0.031 |
|                   | 0.796 | 0.733 |
|                   | 0.87(0.31-2.48) | 0.98(0.89-1.08) |

| Year              | ≤ 2010 | > 2010 |
|-------------------|--------|--------|
|                   | 20     | 20     |
|                   | 0.0%   | 55.2%  |
|                   | 0.961  | 0.002  |
|                   | 0.070  | 0.356  |
|                   | 0.91(0.82-1.01) | 1.06(0.96-1.17) |

| AG VS AA          | Ethnicity          |
|-------------------|--------------------|
|              | Arabian             |
|              | Asian               |
|              | Caucasian           |
|              | Mixed               |

| Cancer type       | Ovarian cancer | Acute lymphoblastic leukemia |
|-------------------|---------------|-----------------------------|
|                   | 4             | 2                           |
|                   | 0.0%          | 0.0%                        |
|                   | 0.998         | 0.631                       |
|                   | 0.145         | 0.981                       |
|                   | 1.09(0.97-1.22) | 1.05(1.01-1.10) |
| Cancer Type               | Sample Size | Frequency | Mean | Median | 95% CI        | p-value | odds ratio     |
|--------------------------|-------------|-----------|------|--------|---------------|---------|---------------|
| Acute lymphoblastic leukemia | 2           | 0.0%      | 0.747| 0.893  | 0.98 (0.78-1.24) | 0.747   |               |
| Breast cancer            | 13          | 42.3%     | 0.054| 0.006  | 1.08 (1.02-1.13) | 0.747   |               |
| Thyroid cancer           | 4           | 33.2%     | 0.213| 0.012  | 1.27 (1.05-1.53) | 0.747   |               |
| Bladder cancer           | 3           | 87.1%     | P<0.001| 0.038 | 0.71 (0.41-1.23) | 0.747   |               |
| Lung cancer              | 3           | 26.7%     | 0.255| 0.132  | 0.87 (0.73-1.04) | 0.747   |               |
| Others                   | 11          | 0.0%      | 0.935| 0.710  | 1.02 (0.92-1.13) | 0.747   |               |

**Method**

| Method            | Sample Size | Frequency | Mean | Median | 95% CI        | p-value | odds ratio     |
|-------------------|-------------|-----------|------|--------|---------------|---------|---------------|
| PCR-RFLP          | 12          | 0.0%      | 0.981| 0.590  | 1.03 (0.93-1.14) | 0.981   |               |
| Sequencing        | 2           | 0.0%      | 0.946| 0.001  | 4.00 (1.79-8.94) | 0.981   |               |
| TaqMan            | 13          | 57.1%     | 0.006| 0.696  | 1.02 (0.92-1.14) | 0.981   |               |
| PCR               | 4           | 72.9%     | 0.011| 0.780  | 1.05 (0.76-1.44) | 0.981   |               |
| ND                | 6           | 35.1%     | 0.173| 0.205  | 1.04 (0.98-1.11) | 0.981   |               |
| Others            | 3           | 0.0%      | 0.577| 0.089  | 1.25 (0.97-1.63) | 0.981   |               |

**Source of control**

| Source of control | Sample Size | Frequency | Mean | Median | 95% CI        | p-value | odds ratio     |
|-------------------|-------------|-----------|------|--------|---------------|---------|---------------|
| HB                | 23          | 56.0%     | 0.001| 0.421  | 1.05 (0.93-1.18) | 0.981   |               |
| PB                | 12          | 0.0%      | 0.803| 0.002  | 1.09 (1.03-1.15) | 0.981   |               |
| Mixed             | 1           | NA        | NA   | NA     | 0.89 (0.62-1.27) | 0.981   |               |
| Nested            | 4           | 0.0%      | 0.989| 0.160  | 0.91 (0.80-1.04) | 0.981   |               |

**Sample size**

| Sample size | Sample Size | Frequency | Mean | Median | 95% CI        | p-value | odds ratio     |
|-------------|-------------|-----------|------|--------|---------------|---------|---------------|
| < 100       | 3           | 31.6%     | 0.232| 0.003  | 2.82 (1.42-5.57) | 0.981   |               |
| > 100       | 37          | 32.9%     | 0.029| 0.153  | 1.04 (0.99-1.10) | 0.981   |               |

**Year**

| Year | Sample Size | Frequency | Mean | Median | 95% CI        | p-value | odds ratio     |
|------|-------------|-----------|------|--------|---------------|---------|---------------|
| ≤ 2010 | 20        | 0.0%      | 0.667| 0.047  | 1.05 (1.00-1.10) | 0.981   |               |
| > 2010 | 20        | 60.8%     | 0.000| 0.278  | 1.08 (0.94-1.25) | 0.981   |               |

**Figures**
Figure 1

Flow chart of study selection.
Figure 2

Funnel plots for the test of publication bias for the five genetic models.