Impact of XRCC2 Arg188His Polymorphism on Cancer Susceptibility: A Meta-Analysis

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Abstract

Background: Association between the single nucleotide polymorphism rs3218536 (known as Arg188His) located in the X-ray repair cross complementing group 2 (XRCC2) gene and cancer susceptibility has been widely investigated. However, results thus far have remained controversial. A meta-analysis was performed to identify the impact of this polymorphism on cancer susceptibility.

Methods: PubMed and Embase databases were searched systematically until September 7, 2013 to obtain all the records evaluating the association between the XRCC2 Arg188His polymorphism and the risk of all types of cancers. We used the odds ratio (OR) as measure of effect, and pooled the data in a Mantel-Haenszel weighed random-effects meta-analysis to provide a summary estimate of the impact of this polymorphism on breast cancer, ovarian cancer and other cancers. All the analyses were carried out in STATA 12.0.

Results: With 30868 cases and 38656 controls, a total of 45 case-control studies from 26 publications were eventually included in our meta-analysis. No significant association was observed between the XRCC2 Arg188His polymorphism and breast cancer susceptibility (dominant model: OR = 0.94, 95%CI = 0.86–1.04, P = 0.232). However, a significant impact of this polymorphism was detected on decreased ovarian cancer risk (dominant model: OR = 0.83, 95%CI = 0.73–0.95, P = 0.007). In addition, we found this polymorphism was associated with increased upper aerodigestive tract (UADT) cancer susceptibility (dominant model: OR = 1.51, 95%CI = 1.04–2.20, P = 0.032).

Conclusion: The Arg188His polymorphism might play different roles in carcinogenesis of various cancer types. Current evidence did not suggest that this polymorphism was directly associated with breast cancer susceptibility. However, this polymorphism might contribute to decreased gynecological cancer risk and increased UADT cancer risk. More preclinical and epidemiological studies were still imperative for further evaluation.

Introduction

As the core component of cell nucleus, DNA suffers from various damaging agents such as chemicals, radiations and some endogenous elements. Under these damages, single strand breaks (SSBs) occur. Subsequently, unrepaired SSBs lead to double strand breaks (DSBs) during the S phase of cell cycle [1]. It has been demonstrated that accumulation of unrepaired DSBs can cause cell death and initiate malignancies [2], which highlights the disorder of DNA repair as the key role in tumorigenesis.

There are several mechanisms repairing DSBs, among which homologous recombination repair (HRR) is the key pathway functioning in the S phase of somatic mammalian cell cycle [2]. Defective HRR has been reported to be closely related to human cancers [3]. During the HRR process, a sister chromatid is provided as a template and the homologous sequence of DNA is aligned. A wide range of crucial molecules have been identified to participate in the HRR process [4]. Recently, researches have revealed that RAD51 paralogs (RAD51B, RAD51C, RAD51D, XRCC2, XRCC3) could serve as central proteins during the HRR process [5].

Coded by X-ray repair cross complementing group 2 (XRCC2) gene, the XRCC2 protein, together with other proteins, RAD51L3 for example [6], forms a complex which plays a critical role in chromosome segregation and apoptotic response to DSBs [7]. Johnson et al. observed over 100-folds of HRR reduction in the XRCC2 deficient hamster cells compared with the parental cells [8], which confirmed the essential function of the XRCC2 protein for the HRR process. Studies have found that single nucleotide polymorphisms (SNPs) in the DNA repair gene...
might modify DNA repair capacity and subsequently influence susceptibility of cancer [9]. Recently, studies have focused on the influence of SNPs in the XRCC2 gene on genomic instability and tumorigenesis. However, the exact function of SNPs in the XRCC2 gene in response to different DNA damaging agents still remained unclear. There is a G to A polymorphism located in exon 3 of the XRCC2 gene resulting in a substitution of histidine (His) for arginine (Arg). Known as Arg188His (R188H, rs3218536), this polymorphism has been widely investigated to explore its potential impact on cancer susceptibility.

A previous meta-analysis reported no significant association between XRCC2 Arg188His polymorphism and breast cancer risk, whereas only one specific cancer type included led to its limitation and the unexplained heterogeneity might reduce the validity of the conclusion [10]. It was widely reported that a single SNP was related to multiple human cancers, which revealed critical common characteristics among mechanisms of different types of cancer [11,12]. Recently, a large number of studies have attempted to identify the association between this polymorphism and other human cancers such as ovarian cancer [13], thyroid cancer [14], and colorectal cancer [15]. However, results of these studies still remain inconsistent rather than conclusive.

As to other SNPs within the XRCC2 gene such as rs718292, rs3218373, and rs6464268, meta-analysis could not be performed due to insufficient published studies. Given the essential role of XRCC2 gene in tumorigenesis, and a relatively small sample size for a single study, we conducted a meta-analysis including all published literature to evaluate the impact of the XRCC2 Arg188His polymorphism on susceptibility of all available types of cancer.

Materials and Methods

Search strategy

A systematic search with no limits was performed in PubMed and Embase databases to identify all the studies on the association between XRCC2 Arg188His polymorphism and cancer risk (last search updated on Sep. 7, 2013). The following search terms were adopted jointly: ‘polymorphism or variant or mutation’, ‘cancer or carcinoma’ and ‘XRCC2’. In addition, cited references of eligible studies were hand-searched as appropriate.

Inclusion and exclusion criteria

Studies consistent with the following criteria were included in our meta-analysis: (1) assessing the association between the XRCC2 Arg188His polymorphism and risk for cancer; (2) case-control studies; (3) sufficient data (a detailed number of genotypes including Arg/Arg, Arg/His and His/His in both the case and the control group); (4) English articles. Correspondingly, studies in accord with any of the following items were excluded: (1) reviews and abstracts; (2) departure from Hardy–Weinberg equilibrium (HWE) detected in controls. Studies recruiting patients during overlapping time in the same hospital were regarded as repeating data; only studies with larger numbers of patients and controls were included.

Data extraction

According to the inclusion criteria above, two investigators (YZH and YCZ) extracted information independently from all eligible studies. Disagreements were resolved by discussion. If consensus could not be reached, we consulted a third reviewer (ZQW). Items extracted from all included studies were listed as follows: first author, year of publication, country of origin, ethnicity, cancer type, source of control groups (population-based or hospital-based), number of cases and controls, genotyping methods, selection criteria for controls minor allele frequency (MAF) and fitness of HWE in controls. For articles including separate case-control studies for different study centers, different ethnic groups or cancer types, data were collected separately whenever possible due to the potential between-study heterogeneity.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used as the measure of effect to evaluate the strength of association between the XRCC2 Arg188His polymorphism and cancer susceptibility. Data were pooled using the Mantel-Haenszel method (P<0.05 was considered as statistically significant). For this polymorphism, the dominant model (Dom:His/His + Arg/His vs. Arg/Arg), recessive model (Rec:His/His vs. Arg/His + Arg/Arg) and additive model (Add: comparison of weights for His/His as ‘2’, Arg/His as ‘1’ and Arg/Arg as ‘0’) were chosen to calculate the pooled ORs.

In view of the potential heterogeneity among studies with different cancer types and various ethnicities, the random-effects model (the DerSimonian and Laird method) was adopted. Heterogeneity among eligible studies was assessed by Cochran’s Q test. The P-value<0.1 indicated significant heterogeneity according to the previous study [16]. We conducted stratified analyses by variables such as cancer types, and ethnicity. Notably, if significant heterogeneity was observed after stratified analysis, a meta-regression analysis was performed to explore the potential origin of heterogeneity. By sequentially excluding every single study, we conducted sensitivity analysis to identify stability of the results and check whether any single study contributed to the heterogeneity significantly.

Considering that enough studies should be included in order to observe the variation trend of the ORs effectively, we performed cumulative meta-analysis as evidence accumulated by time when 10 or more studies were included. Hardy-Weinberg equilibrium (HWE) was assessed by Pearson’s χ2 test, and P<0.05 was regarded as departure from HWE. We checked the symmetry of Begg’s funnel plot and the results of Egger’s test to assess the publication bias. All of the statistical analyses were conducted by STATA (version 12.0; StataCorp,College Station, Tex).

Results

Identification and characteristics of eligible studies

After initial search with duplicates discarded, a total of 225 records of publications were yielded. Following the predefined inclusion and exclusion criteria, eventually 26 articles with 45 case-control studies were included in this meta-analysis (details in Fig.1). The basic characteristics of eligible studies were listed in Table.1. Among these eligible studies, there were 14 case-control studies from 7 articles that investigated association between the Arg188His polymorphism and breast cancer risk [17–23], and 9 studies from 6 articles focused on gynecological cancer such as ovarian cancer [13,23,24],endometrial cancer [25,26] and cervical cancer [27]. Moreover, a wide range of other cancer types were covered by studies including thyroid [14,28,29], pancreatic [30], colorectal [15,31], bladder [32,33], brain [34], skin [35], upper aerodigestive tract (UADT) [36,37] and lung [38,39] cancer. As to ethnicity, most of the eligible studies were performed in Caucasians, except for 1 study in African Americans [20] (Table 1). Furthermore, 3 studies reported association in both smokers and non-smokers [30,32,37]. As shown in Table 1, the source of controls was divided into hospital-based and population-
based, and different selecting criteria for the control group were adopted. The distributions of genotypes for all genetic models were summarized in Table 2.

Quantitative analysis

Given the fact that eligible case-control studies were mainly composed of breast cancer (N = 15) and ovarian cancer (N = 7), which brought about potential bias to the combined analysis; additionally, the considerable inherent heterogeneity among different cancer types and significant statistical heterogeneity we observed (Ph = 0.001) indicated that it might not be informative to pool the data of all types of cancer into a single analysis. Therefore we performed meta-analyses respectively in groups of different cancer types, and the results were summarized in Table 3.

Breast cancer

A total of 17420 breast cancer cases and 17811 controls were included in the meta-analysis. As shown in Table 3, no significant association was observed between the Arg188His polymorphism and breast cancer risk under dominant (OR = 0.94, 95%CI = 0.86–1.04, P = 0.232), recessive (OR = 1.03, 95%CI = 0.95, 95%CI = 0.87–1.04, P = 0.298). Cumulative meta-analysis obtained no significant association as evidence accumulated by time (data not shown).

There was significant heterogeneity when these breast cancer studies were combined under dominant (Ph = 0.013) and additive model (Ph = 0.005). Hence we carried out stratified analysis by ethnicity, but the heterogeneity did not decrease significantly among Caucasians (Table 3). Results of meta-regression analysis showed that neither ethnicity (Coef. = 1.079, P = 0.171) nor source of controls (Coef. = 1.057, P = 0.432) contributed significantly to the heterogeneity. Sensitivity analysis found that ORs did not change significantly when excluding each single study by sequence and verified the stability of our results to some degree (Fig.3). It was worth mentioning that no significant heterogeneity (Dom: Ph = 0.420, Add: Ph = 0.712) was detected when one case-control study [21] ("Pharoah 4" in Table 1) from USA was excluded, which implied that this study might be the origin of the heterogeneity under dominant and additive model.

The Begg’s funnel plot of dominant model seemed symmetrical (Fig. 4), and Egger’s test provided statistical evidence which identified the absence of publication bias (Dom: t = 0.41,
Table 1. Baseline characteristics of eligible case-control studies.

| First Author | N* | Year | Cancer Type | Country | Ethnicity | Source of Control | Cases/Controls | Genotyping Method | Selection criteria for controls |
|--------------|----|------|-------------|---------|-----------|------------------|---------------|------------------|---------------------------------|
| Brooks [17]  | 2008 | Breast cancer | US | Mixed | NA | 602/602 | PCR-RFLP | Age |
| García-Closas [18] | 2006 | Breast cancer | Poland | Caucasian | PB | 1981/2280 | NA | Age |
| Han [19] | 2004 | Breast cancer | US | Mixed | PB | 952/1237 | TaqMan/ABI PRISM | Age |
| Millikan [20] | 1 | 2005 | Breast cancer | US | African American | PB | 765/678 | TaqMan | Age/Ethnicity |
| Millikan [20] | 2 | 2005 | Breast cancer | US | Caucasian | PB | 1268/1134 | TaqMan | Age/Ethnicity |
| Pharoah [21] | 1 | 2006 | Breast cancer | UK | Caucasian | HB | 254/194 | PCR-RFLP | NA |
| Pharoah [21] | 2 | 2006 | Breast cancer | UK | Caucasian | PB | 585/598 | PCR-RFLP | NA |
| Pharoah [21] | 3 | 2006 | Breast cancer | UK | Caucasian | HB | 863/845 | TaqMan | NA |
| Pharoah [21] | 4 | 2006 | Breast cancer | UK | Caucasian | PB | 1865/1402 | TaqMan | Age |
| Pharoah [21] | 5 | 2006 | Breast cancer | UK | Caucasian | PB | 4364/5246 | TaqMan | Region |
| Pharoah [21] | 6 | 2006 | Breast cancer | UK | Caucasian | PB | 973/968 | TaqMan | NA |
| Romanowicz-Makowska [22] | 2012 | Breast cancer | Poland | Caucasian | PB | 790/798 | PCR-RFLP | NA |
| Webb [23] | 1 | 2005 | Breast cancer | Australia | Caucasian/Mixed | PB | 1447/783 | ABI PRISM | Age |
| Webb [23]** | 2 | 2005 | Breast cancer | Australia | Caucasian | PB | 1298/658 | ABI PRISM | Age |
| Auranen [13] | 1 | 2005 | Ovarian cancer | UK | Caucasian | PB | 269/561 | TaqMan/ABI PRISM | Region |
| Auranen [13] | 2 | 2005 | Ovarian cancer | Denmark | Caucasian | PB | 315/404 | TaqMan/ABI PRISM | Age/Ethnicity |
| Auranen [13] | 3 | 2005 | Ovarian cancer | US | Caucasian | PB | 275/1811 | TaqMan/ABI PRISM | Age/Ethnicity |
| Beesley [24] | 2007 | Ovarian cancer | Australia | Caucasian | PB | 923/818 | MALDI-TOF-MS | NA |
| Webb [23] | 3 | 2005 | Ovarian cancer | Australia | Caucasian/Mixed | PB | 524/1118 | ABI PRISM | Age |
| Webb [23]** | 4 | 2005 | Ovarian cancer | Australia | Caucasian | PB | 430/950 | ABI PRISM | Age |
| Han [25] | 2004 | Endometrial cancer | US | Mixed | NA | 217/659 | TaqMan/ABI PRISM | Age |
| Romanowicz-Makowska [26] | 2012 | Endometrial cancer | Poland | Caucasian | NA | 230/236 | PCR-RFLP | NA |
| Pérez [27] | 2013 | Cervical cancer | Argentina | Caucasian | PB | 117/205 | PCR EIA | NA |
| Rajaraman [34] | 1 | 2010 | Glioma | US | Mixed | HB | 342/468 | TaqMan | Age/Ethnicity/Sex/Hospital |
| Rajaraman [34] | 2 | 2010 | Meningioma | US | Mixed | HB | 121/468 | TaqMan | Age/Ethnicity/Sex/Hospital |
| Rajaraman [34] | 3 | 2010 | Acoustic neuroma | US | Mixed | HB | 65/468 | TaqMan | Age/Ethnicity/Sex/Hospital |
| Han [35] | 1 | 2004 | Melanoma | US | Mixed | PB | 214/864 | TaqMan/ABI PRISM | Age/Ethnicity |
| Han [35] | 2 | 2004 | Squamous cell cancer | US | Mixed | PB | 284/864 | TaqMan/ABI PRISM | Age/Ethnicity |
| Han [35] | 3 | 2004 | Basal cell cancer | US | Mixed | PB | 298/864 | TaqMan/ABI PRISM | Age/Ethnicity |
| Benhamou [36] | 1 | 2004 | Oral/Pharyngeal cancer | France | Caucasian | HB | 119/165 | PCR-RFLP | Age/Sex/Hospital |
| Benhamou [36] | 2 | 2004 | Laryngeal cancer | France | Caucasian | HB | 127/165 | PCR-RFLP | Age/Sex/Hospital |
| First Author                        | N* | Year | Cancer Type | Country | Ethnicity | Source of Control | Cases/Controls | Genotyping Method | Selection criteria for controls |
|------------------------------------|----|------|-------------|---------|-----------|-------------------|----------------|------------------|----------------------------------|
| Romanowicz-Makowska [37]          | 2012 | Laryngeal cancer | Poland   | Caucasian | NA       | 253/253           | PCR-RFLP       | NA               |                                  |
| Jiao [30] 1                       | 2008 | Pancreatic Cancer | US       | Caucasian | HB       | 386/418           | PCR-RFLP       | NA               |                                  |
| Jiao [30] 2                       | 2008 | Pancreatic Cancer | US       | Caucasian | HB       | 24/19             | PCR-RFLP       | NA               |                                  |
| Curtin [15]                       | 2009 | Colorectal cancer | US       | Mixed    | PB       | 1209/1380         | SNPlex         | Age/Sex          |                                  |
| Krupa [31]                        | 2011 | Colorectal cancer | Poland   | Caucasian | HB       | 100/100           | PCR-RFLP       | Sex/Age          |                                  |
| Figueroa [33]                     | 2007 | Bladder cancer   | Spain    | Caucasian | HB       | 1138/1129         | TaqMan         | Age/Sex/Ethnicity/Region   |                                  |
| Matullo [32]                      | 2005 | Bladder cancer   | Italy    | Caucasian | HB       | 156/109           | PCR-RFLP       | Age/Region        |                                  |
| Hung [38]                         | 2008 | Lung cancer      | France   | Mixed    | HB/PB    | 2417/3812         | TaqMan/PCR-RFLP | NA               |                                  |
| Zienolddiny [39]                  | 2005 | Lung cancer      | Norway   | Caucasian | PB       | 312/293           | APEX           | Age/Smoke        |                                  |
| Bastos [28]                       | 2009 | Thyroid cancer   | Portugal | Caucasian | PB       | 109/217           | PCR-RFLP       | NA               |                                  |
| Fayaz [29]                        | 2012 | Thyroid cancer   | Iran     | Caucasian | PB       | 50/50             | PCR-HRM        | NA               |                                  |
| García-Quispes [14]               | 2011 | Thyroid cancer   | Spain    | Caucasian | PB       | 397/477           | iPLEX          | NA               |                                  |

* Number of case-control studies separately reported by articles.
** Studies included only in the subgroup meta-analysis of ethnicity.
PB: population-based; HB: hospital-based; NA: not available; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF-MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PCR-HRM: polymerase chain reaction-high resolution melting; APEX: arrayed primer extension; PCR EIA: Polymerase Chain Reaction-Enzyme Immunoassay.

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| First Author | N* | Year | Cancer Type | Case | Control | HWE | MAF in controls |
|--------------|-----|------|-------------|------|---------|-----|----------------|
| Brooks [17]  | 2008 Breast cancer | 602 (515, 83, 4) | 602 (519, 78, 5) | Yes | 0.07 |
| García-Closas [18] | 2006 Breast cancer | 1981 (1763, 212, 6) | 2280 (1983, 281, 16) | Yes | 0.07 |
| Han [19]     | 2004 Breast cancer | 952 (811, 134, 7) | 1237 (1066, 165, 6) | Yes | 0.07 |
| Millikan [20] | 1 2005 Breast cancer | 765 (744, 21, 0) | 678 (653, 25, 0) | Yes | 0.02 |
| Millikan [20] | 2 2005 Breast cancer | 1268 (1084, 176, 8) | 1134 (982, 145, 7) | Yes | 0.07 |
| Pharoah [21] | 1 2006 Breast cancer | 254 (222, 31, 1) | 194 (161, 32, 1) | Yes | 0.09 |
| Pharoah [21] | 2 2006 Breast cancer | 585 (491, 91, 3) | 598 (507, 84, 7) | Yes | 0.08 |
| Pharoah [21] | 3 2006 Breast cancer | 863 (695, 152, 16) | 845 (698, 136, 11) | Yes | 0.09 |
| Pharoah [21] | 4 2006 Breast cancer | 1865 (1662, 198, 5) | 1402 (1177, 214, 11) | Yes | 0.08 |
| Pharoah [21] | 5 2006 Breast cancer | 4363 (3698, 633, 32) | 5246 (4385, 824, 37) | Yes | 0.09 |
| Pharoah [21] | 6 2006 Breast cancer | 973 (818, 145, 10) | 968 (807, 155, 6) | Yes | 0.09 |
| Pharoah [21] | 7 2006 Breast cancer | 712 (587, 122, 3) | 1046 (882, 161, 3) | Yes | 0.08 |
| Romanowicz-Makowska [22] | 2012 Breast cancer | 790 (212, 374, 204) | 798 (202, 406, 190) | Yes | 0.49 |
| Webb [23]    | 1 2005 Breast cancer | 1447 (1251, 187, 9) | 783 (675, 101, 7) | Yes | 0.07 |
| Webb [23]**  | 2 2005 Breast cancer | 1298 (1113, 177, 8) | 658 (562, 90, 6) | Yes | 0.08 |
| Auranen [13] | 1 2005 Ovarian cancer | 729 (629, 98, 2) | 842 (704, 129, 9) | Yes | 0.09 |
| Auranen [13] | 2 2005 Ovarian cancer | 269 (238, 31, 0) | 561 (484, 75, 2) | Yes | 0.07 |
| Auranen [13] | 3 2005 Ovarian cancer | 315 (260, 54, 1) | 404 (331, 68, 5) | Yes | 0.10 |
| Auranen [13] | 4 2005 Ovarian cancer | 275 (251, 23, 1) | 1811 (1538, 267, 6) | Yes | 0.08 |
| Beesley [24] | 2007 Ovarian cancer | 923 (799, 117, 7) | 818 (696, 115, 7) | Yes | 0.08 |
| Webb [23]    | 3 2005 Ovarian cancer | 524 (451, 68, 5) | 1118 (952, 156, 10) | Yes | 0.08 |
| Webb [23]**  | 4 2005 Ovarian cancer | 430 (364, 63, 3) | 950 (802, 140, 8) | Yes | 0.08 |
| Han [25]     | 2004 Endometrial cancer | 217 (183, 32, 2) | 659 (557, 99, 3) | Yes | 0.08 |
| Romanowicz-Makowska [26] | 2012 Endometrial cancer | 230 (111, 58) | 236 (57, 126, 53) | Yes | 0.49 |
| Pérez [27]   | 2013 Cervical cancer | 117 (106, 11) | 205 (165, 40, 0) | Yes | 0.10 |
| Rajaraman [34] | 1 2010 Glioma | 342 (285, 56, 1) | 468 (395, 70, 3) | Yes | 0.08 |
| Rajaraman [34] | 2 2010 Meningioma | 121 (106, 14) | 468 (395, 70, 3) | Yes | 0.08 |
| Rajaraman [34] | 3 2010 Acoustic neuroma | 65 (57, 8) | 468 (395, 70, 3) | Yes | 0.08 |
| Han [35]     | 1 2004 Melanoma | 214 (181, 31) | 864 (730, 127, 7) | Yes | 0.08 |
| Han [35]     | 2 2004 Squamous cell cancer | 284 (239, 42) | 864 (730, 127, 7) | Yes | 0.08 |
| Han [35]     | 3 2004 Basal cell cancer | 298 (257, 38) | 864 (730, 127, 7) | Yes | 0.08 |
| Benhamou [38] | 1 2004 Oral/Pharyngeal cancer | 119 (92, 24) | 165 (142, 22) | Yes | 0.07 |
| Benhamou [36] | 2 2004 Laryngeal cancer | 127 (109, 18, 0) | 165 (142, 22) | Yes | 0.07 |
| Romanowicz-Makowska [37] | 2012 Cervical cancer | 253 (230, 22) | 253 (240, 13) | Yes | 0.03 |
| Jiao [30]    | 1 2008 Pancreatic Cancer | 386 (340, 44) | 418 (368, 49, 1) | Yes | 0.06 |
| Jiao [30]    | 2 2008 Pancreatic Cancer | 24 (21) | 19 (16) | Yes | 0.08 |
| Curtin [15]  | 2009 Colorectal cancer | 1209 (1014, 185, 10) | 1380 (1167, 204, 9) | Yes | 0.08 |
| Krupa [31]   | 2011 Colorectal cancer | 100 (75, 18, 7) | 100 (84, 14, 2) | Yes | 0.09 |
| Figueroa [33] | 2007 Bladder cancer | 1138 (924, 208, 6) | 1129 (908, 208, 13) | Yes | 0.10 |
| Matullo [32] | 2005 Bladder cancer | 156 (133, 22) | 109 (94, 13) | Yes | 0.08 |
| Hung [38]    | 2008 Lung cancer | 2417 (2126, 281) | 3812 (3324, 470) | Yes | 0.18 |
| Zienolddyni [39] | 2005 Lung cancer | 312 (203, 102) | 293 (246, 45) | Yes | 0.08 |
| Bastos [28]  | 2009 Thyroid cancer | 109 (95, 14) | 217 (181, 36, 0) | Yes | 0.08 |
| Fayaz [29]   | 2012 Thyroid cancer | 50 (43, 7) | 50 (45, 5) | Yes | 0.05 |
| García-Quispes [14] | 2011 Thyroid cancer | 397 (314, 79) | 477 (383, 90) | Yes | 0.10 |

** Table 2. Genotype distribution of XRCC2 Arg188His polymorphism.**

* Number of case-control studies separately reported by articles.
**Studies included only in the subgroup meta-analysis of ethnicity.

N: sample size in case or control group; NA: not available; HWE: Hardy–Weinberg equilibrium; MAF: minor allele frequency.
### Table 3. Stratified analysis of the XRCC2 Arg188His polymorphism on cancer susceptibility.

| Variables          | N**  | Case/Control | OR (CI) | P/Ph | OR (CI) | P/Ph | OR (CI) | P/Ph |
|--------------------|------|--------------|---------|------|---------|------|---------|------|
| Breast             | 14   | 17420/17811  | 0.94 (0.86, 1.04) | 0.232/0.013 | 1.03 (0.86, 1.23) | 0.741/0.402 | 0.94 (0.86, 1.04) | 0.251/0.004 |
| Caucasian*         | 11   | 15192/15360  | 0.93 (0.84, 1.03) | 0.158/0.012 | 1.02 (0.86, 1.22) | 0.890/0.270 | 0.93 (0.83, 1.04) | 0.181/0.003 |
| Gynecological      |      |              |         |      |         |      |         |      |
| Ovarian            | 6    | 3035/5554    | **0.83 (0.73, 0.95)** | 0.007/0.407 | 0.64 (0.35, 1.15) | 0.136/0.601 | **0.82 (0.72, 0.93)** | 0.003/0.424 |
| Endometrial        | 2    | 447/895      | 0.95 (0.70, 1.27) | 0.711/0.645 | 1.20 (0.79, 1.81) | 0.399/0.553 | 0.98 (0.73, 1.30) | 0.865/0.654 |
| Cervical           | 2    | 447/895      | 0.95 (0.70, 1.27) | 0.711/0.645 | 1.20 (0.79, 1.81) | 0.399/0.553 | 0.98 (0.73, 1.30) | 0.865/0.654 |
| Others             |      |              |         |      |         |      |         |      |
| UADT               | 3    | 499/583      | **1.51 (1.04, 2.20)** | 0.032/0.370 | 2.11 (0.50, 8.19) | 0.309/0.508 | **1.55 (1.07, 2.24)** | 0.020/0.251 |
| Colorectal         | 2    | 1309/1480    | 1.10 (0.90, 1.35) | 0.354/0.174 | 1.71 (0.80, 3.68) | 0.169/0.253 | 1.34 (0.74, 2.43) | 0.332/0.074 |
| Pancreatic         | 2    | 410/473      | 0.98 (0.65, 1.48) | 0.926/0.768 | 2.17 (0.20, 24.05) | 0.527/0.804 | 0.99 (0.67, 1.51) | 0.991/0.749 |
| Brain              | 3    | 528/1404     | 0.94 (0.70, 1.26) | 0.673/0.529 | 0.78 (0.19, 3.22) | 0.732/0.804 | 0.93 (0.69, 1.24) | 0.601/0.560 |
| Thyroid            | 3    | 556/744      | 1.02 (0.77, 1.36) | 0.897/0.515 | 1.20 (0.30, 4.84) | 0.794/NA | 1.02 (0.77, 1.36) | 0.866/0.509 |
| Lung               | 2    | 2729/4105    | 1.59 (0.54, 4.07) | 0.398/N < 0.001 | 1.19 (0.61, 2.30) | 0.601/0.135 | 1.61 (0.53, 4.86) | 0.398/N < 0.001 |
| Bladder            | 2    | 1294/1238    | 0.96 (0.79, 1.18) | 0.703/0.728 | 0.44 (0.18, 1.08) | 0.073/0.835 | 0.93 (0.76, 1.13) | 0.469/0.831 |
| Skin               | 3    | 796/2592     | 0.96 (0.77, 1.20) | 0.709/0.812 | 1.24 (0.55, 2.82) | 0.605/0.993 | 0.97 (0.78, 1.21) | 0.789/0.819 |

*Subgroup analysis.
**Number of studies included.
P: P-value of association test, Ph: P-value of Q-test for heterogeneity test; NA: not available.
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**Figure 2.** Forest plot for the association of the XRCC2 Arg188His polymorphism with breast cancer risk (dominant model: His/His + Arg/His vs. Arg/Arg). No significant association was observed between the Arg188His polymorphism and susceptibility of breast cancer.
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p = 0.690). Results of recessive and additive model showed no significant publication bias either (data not shown).

Gynecological cancer
Considering 6 of the 10 studies investigated ovarian cancer, and it might generate misleading results for the combined analysis of all types of gynecological cancer, we conducted meta-analysis separately for each type of gynecological cancer. We observed that variant allele carriers (His/His + Arg/His) had significantly lower risk for developing ovarian cancer (OR = 0.83, 95%CI = 0.73–0.95, P = 0.007, Fig.5). However, no significant association was detected between this polymorphism and endometrial cancer (Fig.5). Only one study focusing on cervical cancer reported significant association between the Arg188His polymorphism and decreased susceptibility. Moreover, we did not detect any significant heterogeneity among the eligible studies in each comparison (details in Table 3). For ovarian cancer, the Begg's funnel plot and Egger's test indicated no significant publication bias under the three different genetic models (data not shown). The result of sensitivity analysis for ovarian cancer group found the ORs did not change significantly when every single study were excluded.

Other Cancers
Relatively small number of studies covered other types of cancers. In our study, the UADT cancer consisted of oral, pharyngeal and laryngeal cancer. Significant association was observed between the Arg188His polymorphism and increased susceptibility of UADT cancer (Dom: OR = 1.51, 95%CI = 1.04–2.20, P = 0.032, Fig.6; Add: OR = 1.51, 95%CI = 1.06–2.16, P = 0.023), and no significant heterogeneity was found in any genetic model (Table 3). As for digestive system cancers, we detected no significant association between this polymorphism and either pancreatic or colorectal cancer. In addition, current evidence did not suggest that the Arg188His polymorphism was associated with risk for brain, skin, thyroid, bladder and lung cancer (details in Table 3).

Discussion
As research moved along, the genomic landscape of cancer has been gradually brought into light, and an increasing number of vital genes shared by various cancers, XRCC2 for example, have been revealed in recent years. The XRCC2 Arg188His polymorphism was widely reported to be associated with susceptibility of a wide range of cancers. However, results remained conflicting and a single study might be limited due to a relatively small sample size. Moreover, no conclusive study so far has reported a result.
which covered all available cancer types. Based on all published literature, we performed this meta-analysis to identify the association of the Arg188His polymorphism with cancer susceptibility.

Our study, which derived an asymmetrical distribution of different cancer types, contained 15 studies for breast cancer and 7 for ovarian cancer, generating potential bias to the combined analysis of all cancer types. Moreover, considerable inherent heterogeneity existed among different cancer types, which was confirmed by significant statistical heterogeneity we obtained. Current evidence indicated that the \textit{XRCC2} Arg188His polymorphism might play various roles in different cancer types. Thus it could be of little value to combine all data of different cancer types into a single analysis.

According to our meta-analysis of breast cancer, we observed no significant association between this polymorphism and susceptibility of breast cancer, which accorded with the previous meta-analysis. However, in the previous study, Yu et al [10] reported their result with unexplained significant heterogeneity ($P_h = 0.014$). Furthermore, studies inconsistent with HWE were included in the meta-analysis which might result in potential bias. Limited by factors above, results of previous study should be interpreted with caution. In our study, we detected no significant heterogeneity when one case-control study (Pharoah 4 in Table 1) was excluded, which implied the probability of the removed study being the origin of heterogeneity. We noted that in this case-control study from USA, buccal cells as DNA samples were collected by mail from participants, which could bring in possible inaccuracy. However, insufficient information was provided for further identification of the heterogenous factor of this study. Additionally, cumulative meta-analysis suggested that no significant association was observed as evidence accumulated by time. Theoretically, genetic variants in the \textit{XRCC2} gene could change the regular function of this gene, disturb the DNA repair and increase cancer risk. However, a previous study [40] has identified that the variant allele of this polymorphism could increase resistance to the DNA damage induced by cisplatin, which enlightened protective function of this polymorphism under certain conditions. This finding is to some degree consistent with our paradoxical result of the non-significant association between this polymorphism and breast cancer risk. Future studies should aim at the response of variant allele carriers to specific DNA damage agents of breast cancer.

Figure 5. Forest plot for the subgroup analysis of gynecological cancer (dominant model: Arg/His+His/His vs. Arg/Arg). Significant association was detected between the \textit{XRCC2} Arg188His polymorphism and decreased risk for ovarian cancer and cervical cancer. doi:10.1371/journal.pone.0091202.g005
As for gynecological cancer, we found that variant allele carriers had significantly lower risk for developing ovarian cancer. Our results suggested a protective role of the Arg188His polymorphism, which was apparently paradoxical to the presumable hypothesis. As mentioned above, the previous study [40] indicated that the Arg188His polymorphism might response differently to various damaging agents. It is notable that in one of the studies included in our meta-analysis, Pérez et al [27] adopted HPV adjusted ORs and found the variant allele (A allele) was associated with reduced risk for cervical cancer, which derived a hypothesis that this polymorphism might play a different role in HPV-induced DNA damage. However, our paradoxical findings of gynecological cancer should be interpreted with caution, because only a small number of studies investigating ovarian, endometrial and cervical cancer were finally included in our meta-analysis. A large number of studies with specific damaging factors in consideration should be accumulated to provide further estimate on the association between this polymorphism and gynecological cancer risk.

In our study, we detected significant association between the Arg188His polymorphism and increased UADT cancer, but the result was limited by the small sample size. Considerable caution should be taken into account because only 3 studies were included. Meanwhile, biological heterogeneity is likely to exist among oral cavity, pharyngeal and laryngeal cancer. A few studies investigated other cancer types (brain, skin, thyroid, pancreatic, colorectal cancer); however, we found no significant results in these subgroups. More studies are required to achieve conclusive results for these cancer types and future work should cover cancers that have not been investigated such as gastric, esophageal and hematological cancer.

To our knowledge, this is the most comprehensive meta-analysis which has first investigated the association between the \textit{XRCC2} Arg188His polymorphism and susceptibility of all available cancer types. However, several limitations should be taken into consideration when explaining the results: (1) we only included the studies from selected databases, thus other relevant records might be left out; (2) the number of studies include was relatively small for some cancer types. For example, only one study investigated cervical cancer; (3) due to insufficient information, stratified analysis cannot be conducted by age, sex, treatment, drinking status, exposure to radiation and other factors; (4) lacking of necessary data limited further assessment for gene-gene and loci-loci interaction; (5) as only Caucasian and African American were involved in the pooled analysis, the results might not suit for other ethnicities.

In conclusion, our meta-analysis found that the impact of the \textit{XRCC2} Arg188His polymorphism on susceptibility of different cancers might be diverse. Current evidence did not suggest this polymorphism was directly associated with breast cancer risk. However, we observed that the variant allele carriers might have significantly lower risk for developing gynecological cancer, especially ovarian cancer. Our results should be explained with some caution and be re-evaluated in the future when more studies with larger sample size are conducted.
Supporting Information

Checklist S1  PRISMA checklist. (DOC)

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Author Contributions

Conceived and designed the experiments: ZQW. Performed the experiments: YZH YCZ CWJ. Analyzed the data: XBD QBW MTW THY. Contributed reagents/materials/analysis tools: ZQW YHZ. Wrote the paper: YZH.