Meta-analysis of XRCC1 polymorphism and risk of female reproductive system cancer

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ABSTRACT
Numerous epidemiological studies have evaluated the association between polymorphism in the gene encoding x-ray repair cross complementing 1 (XRCC1) protein and the risk of female reproductive system cancer, but results are inconclusive. To gain a comprehensive picture of available evidence, we searched for relevant studies in the PubMed, EMBASE, Scopus, and Chinese National Knowledge Infrastructure databases up to December 17, 2016. A total of 26 case-control studies were picked out. The pooled odds ratio (OR) with its 95% confidence interval (CI) was calculated to estimate the association. Based on data of all study participants, we did not find a positive association of rs25487 or rs1799782 polymorphism with risk of female reproductive cancer risk. Subgroup analysis, however, identified two alleles as being associated with an increased risk of female reproductive system cancer in Asians: the A allele of rs25487 (heterozygous genetic model, OR 1.16, 95%CI 1.00–1.36), and the T allele of rs1799782 (homozygous model, OR 2.30, 95%CI 1.39–3.82; dominant model, OR 1.28, 95%CI 1.10–1.50; recessive model, OR 1.10, 95%CI 1.33–3.34). Moreover, the AA genotype at rs25489 was determined to be a risk factor for cervical cancer etiology (homozygous model, OR 2.91, 95%CI, 1.17–7.26; recessive model, OR 3.16, 95%CI 1.91–5.24). This meta-analysis suggests that no association between rs25487 or rs1799782 gene polymorphism and risk of female reproductive cancer risk was found. These results should be validated in larger studies.

INTRODUCTION
Female reproductive system cancer, which includes cervical cancer, endometrial cancer, and ovarian cancer, is a major threat to women’s health. In fact, cervical cancer ranks third among all gynecologic cancers in the world [1], 65 new endometrial cancer cases occur annually per 100,000 women between the ages of 65 to 75 [2], and approximately 140,200 new ovarian cancer cases worldwide per year are recorded [3]. Elucidating the etiology of female reproductive system cancer and identifying at-risk populations may allow more effective early detection and perhaps even prevention.

The causes of these cancers remain poorly understood. Infection with oncogenic human papilloma virus (HPV) is a risk factor in tumorigenesis [4], but many HPV carriers do not develop cervical cancer, indicating that there must be other cancer risk factors, such as genetic and environmental factors. One possible genetic factor may be polymorphism in the gene encoding x-ray repair cross complementing 1 (XRCC1) protein. The gene is located on chromosome 19 (19q13.2), and the expressed protein is involved in the base excision repair (BER) pathway [5, 6], which helps correct errors during DNA replication and recombination as well as preserve genome integrity [7]. Functional single-nucleotide polymorphisms (SNPs) in XRCC1 have been linked to
development of esophageal squamous cell carcinoma [8], lung cancer [9], pancreatic cancer [10], breast cancer [11], colorectal cancer [12], and gastric cancer [13]. While more than 300 XRCC1 SNPs have been described in the dbSNP database, three functional SNPs have been extensively studied, all of which cause amino acid substitutions in the encoded protein: rs25487 [Arg399Gln], rs1799782 [Arg194Trp] and rs25489 [Arg280His].

Associations between XRCC1 SNPs and risk of female reproductive system cancer are unclear, because the several molecular epidemiologic studies conducted so far have been inconclusive. This lack of clarity may reflect the relatively small statistical power in individual studies, as well as heterogeneity in genetic backgrounds of study participants. Therefore we performed this meta-analysis to comprehensively assess available evidence on the association between XRCC1 polymorphism and risk of female reproductive system cancer.

RESULTS

Study characteristics

Systematic search of the PubMed, EMBASE and China National Knowledge Infrastructure (CNKI) databases identified 157 potentially relevant studies (Figure 1). Further screening allowed elimination of all but 31 studies, which were read in full. In the end, 26 case-control studies were included in this study (Table 1): data on rs25487 were reported in 24 studies involving 4,265 cases and 5,495 controls; data on rs1799782 were reported in 15 studies involving 2,672 cases and 3,578 controls; and data on rs25489 were reported in 5 studies with 907 cases and 1,416 controls. The various ethnic groups involved in the studies were divided into two categories: Asian or Non-Asian, with the latter including Caucasian, Latino, and mixed.

Of the 24 studies related to rs25487, 16 focused on cervical cancer [14–29], 5 on endometrial cancer [30–34], and 3 on ovarian cancer [35–37]. The ethnic group was Asian in 11 studies and Non-Asian in the others. Of the 15 studies related to rs1799782, 10 focused on cervical cancer [16–20, 25, 27, 28], 3 on endometrial cancer [35,37,38], and 2 on ovarian cancer [30,31]. The ethnic group was Asian in 7 studies and Non-Asian in 8 studies. Of the 5 studies related to rs25489, all focused on cervical cancer. The population was Asian in 4 studies and Non-Asian in one study.

Across all studies, the distribution of genotypes in controls was mostly in agreement with Hardy-Weinberg equilibrium (HWE), except in 5 studies on rs25487 [6, 15, 17, 18, 36], 5 studies on rs1799782 [15–18, 26] and 2 studies on rs25489 [15, 39].

Quantitative data synthesis

Across the entire pooled study population, a significant association was not found between rs25487 and risk of female reproductive system cancer (Table 2). In the subgroup of Asian participants, however, we detected a significant association of the A variant at rs25487 with increased risk of female reproductive system cancer (GA vs. GG, OR 1.16, 95%CI 1.00–1.36). This association disappeared when we excluded 5 studies that deviated from HWE, instead appearing in the subgroup of Non-Asian participants (AA vs. GA/GG, OR 1.61, 95%CI 1.41–1.85). Subgroup analysis by cancer type indicated an association between the A allele at rs25487 and increased risk of cervical cancer (AA vs. GA/GG, OR 1.22, 95%CI 1.05–1.41), endometrial cancer (AA vs. GG, OR 2.16, 95%CI 1.00–4.67) and ovarian cancer (AA vs. GA/GG, OR 2.01, 95%CI 1.70–2.38). The significant associations with cervical cancer and ovarian cancer disappeared after removing studies that deviated from HWE.

Across the entire pooled study population, no association was found between rs1799782 and risk of female reproductive system cancer (Table 2). In subgroup analysis by ethnicity, the T variant was significantly associated with increased risk of female reproductive system cancer in Asians (TT vs. CC, OR 2.30, 95%CI 1.39–3.82; TT/CT vs. CC, OR 1.28, 95%CI 1.10–1.50; TT vs. CT/CC, OR 2.11, 95%CI 1.33–3.34). This association remained significant after excluding 5 studies that deviated from HWE(TT vs. CC, OR 1.67, 95%CI 1.33–2.09; TT/CT vs. CC, OR 1.12, 95%CI 1.04–1.21; TT vs. CT/CC, OR 1.65, 95%CI 1.30–2.09). In subgroup analysis by tumor type, the T allele was associated with increased risk of cervical cancer (TT vs. CT/CC, OR 1.30, 95%CI 1.07–1.59), and this association remained significant after excluding studies that deviated from HWE (TT vs. CC, OR 1.62, 95%CI 1.26–2.07; TT/CT vs. CC, OR 1.10, 95%CI 1.01–1.20; TT vs. CT/CC, OR 1.63, 95%CI 1.26–2.11). The same T variant increased risk of endometrial cancer based on all study participants (TT vs. CC, OR 2.50, 95%CI 1.16–5.37) as well as based on only studies consistent with HWE (TT vs. CC, OR 2.00, 95%CI 1.15–3.49).

Data on rs25489 SNPs were limited to cervical cancer studies. Meta-analysis suggested that the A variant was associated with increased risk of this cancer (AA vs. GG, OR 2.91, 95%CI 1.17–7.26; AA vs. GA/GG, OR 2.01, 95%CI 1.70–2.38).

Heterogeneity and sensitivity analyses

Significant heterogeneity across studies was observed in the meta-analysis of the association between the A variant at rs25487 and risk of female reproductive system cancer (homzygous model, F = 81.6, P = 0.000; heterozygous model: F = 54.4, P = 0.001; dominant model: F = 67.2, P < 0.001; recessive model: F = 85.1, P < 0.001). Similarly, significant heterogeneity across studies was observed in the meta-analysis of the association between the T allele at rs1799782 and cancer risk (homzygous model, F = 84.7, P < 0.001; heterozygous model, F = 52.5, P = 0.011; dominant model, F = 77.1, P
| First author | Year | Country | Ethnicity | Cancer type | Sourcecon | Source of DNA | Genotyping method | Case | Control | HWEcon |
|--------------|------|---------|-----------|-------------|-----------|---------------|------------------|------|---------|--------|
| Sobczuk      | 2012 | Poland  | Caucasian | Endometrial | HB        | Blood         | PCR-RFLP         | 94  | 114     | 0.161  |
| Hosono       | 2013 | Japan   | Asian     | Endometrial | HB        | Blood         | PCR-RFLP         | 91  | 261     | 0.681  |
| Romanowicz-Makowska | 2013 | Poland  | Caucasian | Endometrial | HB        | Cervical specimens | PCR-RFLP         | 150 | 150     | 0.992  |
| Cincin       | 2012 | Turkey  | Caucasian | Endometrial | HB        | Blood         | PCR-RFLP         | 104 | 158     | 0.396  |
| Samulak      | 2011 | Poland  | Caucasian | Endometrial | HB        | Cervical specimens | PCR-RFLP         | 456 | 300     | 0.505  |
| Malisic      | 2015 | Serbia  | Caucasian | Ovarian     | PB        | Cervical specimens | PCR-RFLP         | 50  | 78      | 0      |
| Monteiro     | 2014 | Brazil  | Mixed     | Ovarian     | HB        | Blood         | PCR-RFLP         | 70  | 70      | 0.676  |
| Khokhrina    | 2015 | Russia  | Caucasian | Ovarian     | HB        | Blood         | PCR-RFLP         | 104 | 298     | 0.908  |
| Fan          | 2013 | China   | Asian     | Cervical    | HB        | Blood         | MAMA-PCR         | 235 | 350     | 0      |
| Wang         | 2009 | USA     | Latino    | Cervical    | PB        | Blood         | Taqman           | 457 | 442     | 0.761  |
| Wu           | 2003 | Taiwan  | Asian     | Cervical    | PB        | Blood         | PCR-RFLP         | 100 | 196     | 0.531  |
| Settheetham-Ishida | 2011 | Thailand | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 111 | 118     | 0.539  |
| Huang        | 2007 | China   | Asian     | Cervical    | HB        | Blood         | MA-PCR           | 539 | 800     | 0.104  |
| Farkasova    | 2008 | Slovakia| Caucasian | Cervical    | HB        | Blood         | PCR-RFLP         | 18  | 30      | 0.179  |
| Djansugurova | 2013 | Kazakhstan | Mixed     | Cervical    | HB        | Blood, cervical specimens | PCR-RFLP         | 217 | 160     | 0      |
| Zhang        | 2012 | China   | Asian     | Cervical    | HB        | Blood         | SNPstream        | 80  | 177     | 0.538  |
| Barbisan     | 2011 | Argentina | Latino    | Cervical    | HB        | Cervical specimens | PCR-RFLP         | 103 | 114     | 0.49   |
| Jiang        | 2009 | China   | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 456 | 503     | 0.482  |
| Niwa         | 2005 | Japan   | Asian     | Cervical    | HB        | Buffy coat    | PCR-RFLP         | 131 | 320     | 0.088  |
| Xiao         | 2010 | China   | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 162 | 183     | 0.116  |
| Roszak       | 2011 | Poland  | Caucasian | Cervical    | PB        | Blood         | PCR-RFLP         | 189 | 308     | 0.371  |
| Ma           | 2011 | China   | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 200 | 200     | 0.061  |
| Alsbeih      | 2013 | SaudiArabia | Asian     | Cervical    | HB        | Blood         | Sequencing       | 100 | 100     | 0.04   |
| Bajpai       | 2016 | India   | Indian    | Cervical    | PB        | Blood, cervical specimens | PCR-RFLP         | 68  | 65      | 0.036  |

**rs1799782(Arg94T trạng)**

| First author | Year | Country | Ethnicity | Cancer type | Sourcecon | Source of DNA | Genotyping method | Case | Control | HWEcon |
|--------------|------|---------|-----------|-------------|-----------|---------------|------------------|------|---------|--------|
| Michalska    | 2015 | Poland  | Caucasian | Ovarian     | HB        | Cervical specimens | PCR-RFLP         | 720 | 720     | 0.053  |
| Monteiro     | 2014 | Brazil  | Mixed     | Ovarian     | HB        | Blood         | PCR-RFLP         | 70  | 70      | 0.69   |
| Khokhrina    | 2012 | Russia  | Caucasian | Ovarian     | HB        | Blood         | PCR-RFLP         | 104 | 298     | 0.562  |
| Sobczuk      | 2012 | Poland  | Caucasian | Endometrial | HB        | Blood         | PCR-RFLP         | 94  | 114     | 0.588  |
| Hosono       | 2013 | Japan   | Asian     | Endometrial | HB        | Blood         | PCR-RFLP         | 91  | 251     | 0.525  |
| Fan          | 2013 | China   | Asian     | Cervical    | HB        | Blood         | MAMA-PCR         | 235 | 350     | 0      |
| Wu           | 2003 | Taiwan  | Asian     | Cervical    | PB        | Blood         | PCR-RFLP         | 100 | 196     | 0.196  |
| Settheetham-Ishida | 2011 | Thailand | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 111 | 118     | 0.023  |
| Huang        | 2007 | China   | Asian     | Cervical    | HB        | Blood         | MA-PCR           | 539 | 800     | 0.731  |
| Farkasova    | 2008 | Slovakia| Caucasian | Cervical    | HB        | Blood         | PCR-RFLP         | 17  | 30      | 0.543  |
| Djansugurova | 2013 | Kazakhstan | Mixed     | Cervical    | HB        | Blood, cervical specimens | PCR-RFLP         | 217 | 160     | 0.001  |
| Zhang        | 2012 | China   | Asian     | Cervical    | HB        | Blood         | SNPstream        | 80  | 117     | 0.434  |
| Barbisan     | 2011 | Argentina | Latino    | Cervical    | HB        | Cervical specimens | PCR-RFLP         | 103 | 114     | 0      |
| Wang         | 2010 | China   | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 123 | 175     | 0.849  |
| Bajpai       | 2016 | India   | Indian    | Cervical    | PB        | Blood, cervical specimens | PCR-RFLP         | 68  | 65      | 0.001  |

**rs25489(Arg280His)**

| First author | Year | Country | Ethnicity | Cancer type | Sourcecon | Source of DNA | Genotyping method | Case | Control | HWEcon |
|--------------|------|---------|-----------|-------------|-----------|---------------|------------------|------|---------|--------|
| Wu           | 2003 | Taiwan  | Asian     | Cervical    | PB        | Blood         | PCR-RFLP         | 100 | 196     | 0.071  |
| Huang        | 2007 | China   | Asian     | Cervical    | HB        | Blood         | MA-PCR           | 539 | 800     | 0.463  |
| Zhang        | 2012 | China   | Asian     | Cervical    | HB        | Blood         | SNPstream        | 80  | 177     | 0.494  |
| Wang         | 2010 | China   | Asian     | Cervical    | HB        | Blood         | PCR-RFLP         | 123 | 175     | 0.043  |
| Bajpai       | 2016 | India   | Indian    | Cervical    | PB        | Blood, cervical specimens | PCR-RFLP         | 65  | 68      | 0      |

Sourcecon: Source of control. HWEcon: Hardy–Weinberg equilibrium in controls. PB, population-based; HB, hospital-based.
< 0.001; recessive model: $I^2 = 82.5, P < 0.001$). Among studies used in meta-analyses involving rs25489, we found moderate heterogeneity in the homozygous model ($I^2 = 54.3, P = 0.067$) and dominant model ($I^2 = 80.5, P < 0.001$), but no significant heterogeneity in the heterozygous or recessive models.

Then we performed sensitivity analysis, in which we recalculated the meta-analysis after deleting each study systematically. The results were not substantially different after excluding any single study, indicating the robustness of our original meta-analyses.

**DISCUSSION**

XRCC1 is the first protein to participate in the BER pathway, acting as a scaffold for other DNA repair proteins, such as DNA ligase IIIa, DNA polymerase β and poly (ADP-ribose) polymerase [40]. The XRCC1 SNPs rs25487, rs1799782, and rs25489 have been linked to susceptibility for several types of cancer, but it is unclear whether this is also true for female reproductive system cancer. The present meta-analysis suggests that as in other cancers, XRCC1 polymorphism may also influence tumorigenesis in the female reproductive system.

The present study may be the first quantitative meta-analysis of XRCC1 polymorphism and risk of female reproductive system cancer. Previous meta-analyses focused only on cervical cancer risk [41–45], and they reported that rs25487 and rs1799782 were associated with increased risk in Asian populations. The present meta-analysis extended this finding by showing that in Asians, the A allele of rs25487 and T allele of rs1799782 are associated with increased risk of female reproductive system cancer. These findings should be verified in larger studies, especially since the association with rs25487 disappeared in Asians and appeared in Non-Asians after we excluded studies deviating from HWE.

We did not observe a significant association between XRCC1 rs25489 and risk of ovarian cancer, even though estrogens and their metabolites damage DNA by forming...
Table 2: Meta-analysis of the associations between XRCC1 polymorphisms and risk of female reproductive system cancer

| Variable          | N   | Cases/controls | Homozygous genetic model | Heterozygous genetic model | Dominant genetic model | recessive genetic model |
|-------------------|-----|----------------|--------------------------|---------------------------|------------------------|------------------------|
|                   |     |                | OR (95 % CI)              | Phet F                    | OR (95 % CI)            | Phet F              |
| rs25487 (Arg399Gln)|     |                | AA vs. GG                | 1.34(0.92,1.97)           | 0.000 81.6             | 1.06(0.92,1.22) 0.001 54.4 |
| All studies       | 24  | 4265/5495      |                          |                           |                        |                       |
| Ethnicity         |     |                |                          |                           |                        |                       |
| Asian             | 11  | 2185/3208      | 1.49(0.90,2.45)          | 0.000 73.6                | 1.16(1.00,1.16) 0.121 34.7 |
| Non-Asian         | 13  | 2080/2287      | 1.24(0.68,2.24)          | 0.000 86.5                | 0.96(0.76,1.22) 0.004 59.7 |
| Tumor type        |     |                |                          |                           |                        |                       |
| Cervical          | 16  | 3146/4066      | 1.36(0.87,2.12)          | 0.000 80.5                | 1.10(0.93,1.30) 0.000 58.5 |
| Endometrial       | 5   | 895/983        | 2.16(1.00,4.67)          | 0.006 72                  | 1.02(0.67,1.53) 0.022 65.1 |
| Ovarian           | 3   | 224/446        | 0.63(0.21,1.93)          | 0.026 72.5                | 0.92(0.65,1.31) 0.921 0.0 |
| Consistent with HWE | 19  | 3595/4742      | 1.35(0.94,1.92)          | 0.000 75.6                | 1.07(0.90,1.27) 0.000 63.7 |
| Asian             | 9   | 1855/2758      | 1.17(0.76,1.80)          | 0.009 60.7                | 1.18(0.99,1.42) 0.073 44.2 |
| Non-Asian         | 10  | 1745/1984      | 1.95(0.90,2.80)          | 0.000 83.1                | 0.97(0.72,1.30) 0.001 69.7 |
| Tumor type (consistent with HWE) |     |                |                          |                           |                        |                       |
| Cervical          | 12  | 2526/3391      | 1.17(0.80,1.71)          | 0.000 69.6                | 1.11(0.90,1.38) 0.000 69.3 |
| Endometrial       | 5   | 895/983        | 2.16(1.00,4.67)          | 0.006 72                  | 1.02(0.67,1.53) 0.022 65.1 |
| Ovarian           | 2   | 560/368        | 1.64(0.55,1.99)          | 0.582 0.0                 | 0.95(0.64,1.41) 0.950 0.0 |
| rs179782 (Arg194Trp) | 18 | 2672/3578  | 1.19(0.67,2.13)          | 0.000 84.7                | 1.02(0.84,1.23) 0.011 52.5 |
| All studies       | 15  |                |                           |                           |                        |                       |
| Ethnicity         |     |                |                          |                           |                        |                       |
| Asian             | 7   | 1279/2007      | 2.38(1.39,4.71)          | 0.016 61.4                | 1.16(0.99,1.34) 0.588 0.0 |
| Non-Asian         | 8   | 1393/1571      | 0.42(0.14,1.26)          | 0.000 83.5                | 0.76(0.48,1.19) 0.003 70.4 |
| Tumor type        |     |                |                          |                           |                        |                       |
| Cervical          | 10  | 1593/2125      | 1.20(0.50,2.87)          | 0.000 88.7                | 1.02(0.79,1.32) 0.008 61.4 |
| Endometrial       | 3   | 185/365        | 2.50(1.16,5.37)          | /                         | 1.01(0.36,2.87) 0.079 67.5 |
| Ovarian           | 2   | 894/1088       | 0.96(0.72,1.38)          | 0.789 0.0                 | 0.93(0.62,1.38) 0.222 33.6 |
| Consistent with HWE | 10  | 1993/2771      | 1.45(0.96,2.19)          | 0.017 58.9                | 1.08(0.91,1.28) 0.276 18.8 |
| Asian             | 5   | 933/1539       | 1.67(1.33,2.09)          | 0.224 29.6                | 1.08(0.98,1.18) 0.311 16.3 |
| Non-Asian         | 5   | 1005/1232      | 0.99(0.85,1.13)          | 0.782 0.0                 | 1.00(0.92,1.10) 0.227 30.9 |
| Tumor type (consistent with HWE) |     |                |                          |                           |                        |                       |
| Cervical          | 5   | 859/1318       | 1.62(1.26,2.07)          | 0.156 42.5                | 1.06(0.95,1.17) 0.337 11.1 |
| Endometrial       | 3   | 185/365        | 2.00(1.15,3.49)          | /                         | 1.12(0.89,1.41) 0.120 58.6 |
| Ovarian           | 2   | 894/1088       | 0.98(0.85,1.13)          | 0.782 0.0                 | 1.01(0.93,1.11) 0.257 26.5 |
| rs25489 (Arg280His) | 5   | 907/1416       | 1.71(1.17,2.67)          | 0.067 54.3                | 0.98(0.80,1.21) 0.558 0.0 |
| All studies       | 5   |                |                           |                           |                        |                       |
| Ethnicity         |     |                |                          |                           |                        |                       |
| Asian             | 4   | 842/1348       | 1.73(0.87,3.43)          | 0.524 0.0                 | 0.97(0.82,1.15) 0.683 0.0 |
| Non-Asian         | 1   | 65/68          | 3.10(1.85,5.20)          | /                         | 1.81(0.68,4.86) / /   |

N: Number of studies. P<sub>het</sub>: P value for heterogeneity test. HWE: Hardy–Weinberg equilibrium.

bulky DNA adducts [46], which are normally repaired by the BER pathway. It is possible that our negative results reflect limited sample size. Further studies are needed to verify our findings.

To ensure results as reliable as possible, we analogized the studies in our meta-analysis to approximate randomized controlled trials. At the same time, our study does have several limitations. Our results were based on OR analyses that did not adjust for age, family history, gender, reproductive history, or other biological factors that might influence risk of female reproductive system cancer. Similarly, we did not take into account potential effects of gene-environment interaction. Therefore further work is needed before definitive conclusions can be drawn about these three XRCCI SNPs and risk of female reproductive system cancer.

Despite these limitations, our data provide up-to-date evidence from a comprehensive review of the
literature that the A allele of rs25487 and T allele of rs1799782 are low-penetration risk factors for female reproductive system cancer in Asians. It may be that these alleles translate to weaker interaction between XRCC1 and other repair proteins, thereby reducing DNA repair capacity [47]. Our findings add to the growing evidence that polymorphism in DNA repair genes can destabilize the genome and increase tumor susceptibility [32].

**MATERIALS AND METHODS**

**Literature search strategy**

We performed a comprehensive literature search in the PubMed, EMBASE, Scopus, and CNKI databases up to December 17, 2016. The following search strings were used: “X-ray repair cross complementing protein1” or “XRCC1”; “polymorphisms” or “variants”; “carcinoma” or “cancer” or “malignancy” or “neoplasm” or “tumour” or “tumor”; “cervical” or “endometrial” or “ovarian” or “vaginal” or “vulvar” or “fallopian tube” or “female reproductive system”. The reference lists of relevant articles were also searched manually to identify additional eligible studies. When different studies presented overlapping data, we included only the larger study.

**Inclusion and exclusion criteria**

Studies included in this meta-analysis had to be case-control or genome-wide association studies for which full text was available and that reported adequate data on genotype frequencies for cases and controls. Studies were excluded if they reported data overlapping with those of a larger study.

**Data extraction**

Two investigators (N.-N.Y and Y.-F.H) independently extracted the following data from all eligible publications: the first author’s name, year of publication, country of origin, ethnicity, study type (retrospective or prospective), source of control subjects (population-based [PB] or hospital-based [HB]), DNA source (e.g., blood, lymphocytes or buffy coat), genotyping method, total numbers of cases and controls and \( P \) value for HWE. Conflicts were resolved by consensus among all authors.

**Statistical analysis**

Agreement between study results and HWE predictions was tested using the goodness-of-fit \( \chi^2 \) test, with the threshold for HWE defined as \( P > 0.05 \). Strength of association between \( XRCC1 \) SNPs and cancer risk was assessed using odds ratios (ORs) and associated 95% confidence intervals (95%CI). Four different genetic models were conducted to detect the association: homozygous model (VV vs. WW), heterozygous model (WV vs. WW), dominant genetic model (VV+WV vs. WW) and recessive model (VV vs. WW+WV), with W and V representing the wild and variant alleles of each SNP. Heterogeneity across studies was assessed using a \( \chi^2 \)-test-based \( Q \) statistic test, and the level of heterogeneity was quantified using the \( I^2 \) test. When heterogeneity across studies was obvious (\( P \geq 0.05 \) or \( I^2 < 50\% \)) [48], the random effects model was used to meta-analyze data from different studies. Otherwise, the fixed effects model was adopted [49]. All studies were analogized into interim randomized controlled clinical trials in order to control for type I and type II error.

Subgroup analyses were carried out based on ethnicity, tumor type and HWE[50]. Sensitivity analysis was performed in which we recalculated the meta-analysis after deleting each study systematically. Publication bias was investigated using Beggs’s and Egger’s test [51], with significant risk of bias defined as \( P < 0.05 \). All statistical analyses were performed using STATA 11.0 (Stata Corp, College Station, Texas USA). All \( P \) values were two-sided.

**Authors’ contributions**

Guarantors of integrity of entire study, J.F.J.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, N.N.Y., Y.F.H.; statistical analysis, N.N.Y., Y.F.H.; and manuscript editing, N.N.Y., J.S., J.F.J.

**CONFLICTS OF INTEREST**

None.

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