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Review

# *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer susceptibility: Evidence from 80 studies

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## Abstract

Emerging epidemiological researches have been performed to assess the association of *ESR1* PvuII (rs2234693 T>C) polymorphism with the risk of cancer, yet with conflicting conclusions. Therefore, this updated meta-analysis was performed to make a more accurate evaluation of such relationship. We adopted EMBASE, PubMed, CNKI, and WANFANG database to search relevant literature before January 2018. Odds ratios (ORs) and 95% confidence intervals (CIs) were employed to estimate the relationship strengths. In final, 80 studies (69 publications) involving 26428 cases and 43381 controls were enrolled. Our results failed to provide significant association between overall cancer risk and PvuII polymorphism under homozygous (TT vs. CC) and heterozygous (TT vs. CT) models. Statistically significant relationship was only observed for PvuII polymorphism in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99). Stratification analysis by cancer type suggested that T genotype significantly decreased prostate cancer risk (TT vs. CC: OR=0.79, 95% CI=0.66-0.94; T vs. C: OR=0.89, 95% CI=0.82-0.98), Leiomyoma risk (T vs. C: OR=0.82, 95% CI=0.68-0.98), and HCC risk (TT vs. CC: OR=0.45, 95% CI=0.28-0.71; T vs. C: OR=0.67, 95% CI=0.47-0.95). Furthermore, significantly decreased risk was also found for Africans, population-based and hospital-based studies in the stratified analyses. These results suggest that *ESR1* PvuII (rs2234693 T>C) polymorphism may only have little impact on cancer susceptibility. In the future, large-scale epidemical studies are warranted to verify these results.

Key words: meta-analysis, *ESR1*, PvuII, polymorphism, cancer risk

## Introduction

Worldwide, cancer still ranks the number one killer that threatens people's life. Approximately 14.1 million new cancer cases and 8.2 million cancer-caused deaths occurred globally in 2013 [1]. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States [2]. By now, the definitive etiology of cancer remains unknown. However, a myriad of evidence has suggested that cancer is a complex disease caused by both genetic and environmental factors [3, 4]. Numerous functional polymorphisms have been found to be implicated in the development of cancers [5-7].

Previous researches have reported that hormonal factors play crucial roles in the development of some cancers. Common genetic variants in hormonal-related genes were associated with cancer susceptibility [8]. Among them, estrogen receptor (ER) was the most related-hormone in cancer risk. Estrogen receptor (ER) has two forms, which is alpha and beta [9]. Estrogen receptor-α plays a critical role in mediating hormonal response in estrogen-sensitive tissues. It consists of several domains important for hormone regulation, activation of transcription and DNA binding. Evidence points to estrogen receptor-α as the main receptor correlated to

initiation of cancer [10]. Estrogen receptor-α, a transcription factor, is encoded by the *ESR1* gene.

The *ESR1* gene, comprises of 8 exons and 7 introns, is located on chromosome 6q25.1. Several SNPs of *ESR1* gene have been identified to influence the risk of cancer, but the most popular studied SNP is *ESR1* PvuII (rs2234693 T>C) polymorphism [11]. Although increasing studies have been performed, the conclusions of the roles of *ESR1* PvuII (T>C) polymorphism in cancer risk are conflicting. The inconsistent conclusions between *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk may be due to the limitations in the sample size of the corresponding studies or the inadequate statistical power in genetic studies with complex characteristics. Several meta-analyses regarding this issue have been performed to resolve the conflicting situation but somehow failed. With the aim to solve such embarrassment, we conducted this comprehensive meta-analysis by adopting all published articles.

## Materials and methods

### Publication search

We first inputted the following key words: "single nucleotide polymorphism or polymorphism or variant or SNP" and "*ESR1* or *ESR*α or Estrogen Receptor α or Estrogen Receptor 1", and "cancer or tumor or neoplasm or carcinoma)" in database of PubMed and EMBASE. In addition, we also searched the Chinese database CNKI and WANFANG to include more eligible studies. Further, additional studies were also manually extracted from the references of the above obtained publications. The date of the final literature search was set on January 2018. We did not set any language publication restrictions here. The article will be considered as different studies if it contains more than two ethnicities. If the searched articles have overlapping data, the largest one will be selected.

### Eligibility criteria

The evaluating publications in this meta-analysis should fulfill all the following requirements: 1) unrelated case-control studies; 2) original epidemiological studies; 3) analyzing the relationship between *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk; 4) enough data to obtain odds ratios (ORs) and 95% confidence intervals (CIs); 5) articles written in English or in Chinese.

### Data extraction

Two authors separately extracted data by screening all eligible studies. They collected the information regarding first author's surname, country, publication year, ethnicity, genotyping methods, the source of controls, and numbers of cases and controls with CC, CT and TT genotypes. All the disagreed information was settle down after fully discussed by the two authors.

### Statistical methods

Hardy-Weinberg equilibrium (HWE) in the controls was determined using goodness-of-fit $\chi^2$ test. $P<0.05$ was considered as departure from HWE. Three genetic models, homozygous model (TT vs. CC), heterozygous model (TT vs. CT), and allele comparison (T vs. C), were applied to assess the association between *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk. The strength of such association was assessed by calculating ORs with the corresponding 95% CIs. Stratification analyses were also conducted by ethnicity, cancer type, source of control, and HWE in controls, in all studies. Chi square-based *Q*-test was adopted to monitor between-study heterogeneity. The fixed-effects model (the Mantel-Haenszel method) was chosen to estimate the pooled OR, if the studies were homogeneous ($P>0.10$ for the *Q* test). Otherwise, the random-effects model (the DerSimonian and Laird method) was used. Sensitivity analysis was conducted by excluding each study individually and re-calculating the ORs and 95% CIs. Begg's funnel plot and Egger's linear regression were used to evaluate whether there exists publication bias [12, 13]. The asymmetric plot and *P* value less than 0.5 was considered as the existence of publication bias. We also conducted quality assessment to detect the quality of each study using the quality assessment criteria [14]. The version 11.0 STATA software was adopted to perform all statistical analysis (Stata Corporation, College Station, TX). All the statistics were two-sided with *P* value of <0.05 as significant findings.

## Results

### Study characteristics

Our first research in databases identified 185 candidate publications. After screening the title and abstract, we kept 64 publication s in the analysis [15-78]. Moreover, we further extracted 5 articles from the references of the retrieval articles [79-83]. The flow chart of screening process was graphically shown in **Figure 1**. In final, 80 studies (69 publications) with 26428 cases and 43381 controls were included in the pooled analysis (**Table 1**). Among them, 38 studies focused on Asians, 36 on Caucasians, 3 on Africans, 1 on Hispanics and 1 on non-Hispanic Caucasians, 1 on Hispanic Caucasians. 44 studies were hospital-based design, 36 were population-based design. The controls' genotype frequencies were in agreement with HWE ($P>0.05$) in 74 studies, except for 6 studies.

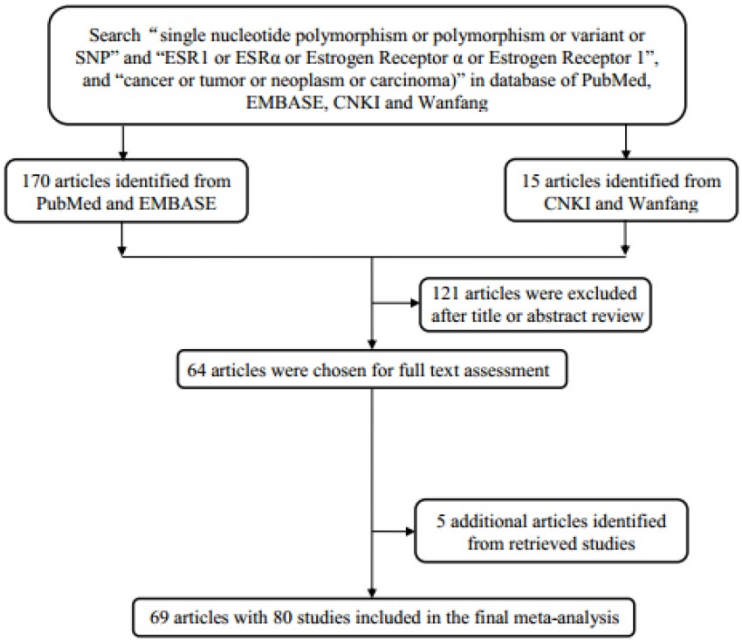


**Figure 1.** Flowchart of study selection process.

**Table 1.** The baseline characteristics of all qualified studies in this meta-analysis

| Surname | Year | Country | Ethnicity | Cancer type | Control Source | Genotype method | Case | | | | Control | | | | HWE | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | TT | CT | CC | All | TT | CT | CC | All | | |
| Modugno | 2001 | USA | Caucasian | Prostate | PB | PCR | 26 | 34 | 21 | 81 | 85 | 109 | 43 | 237 | 0.438 | 8 |
| Massart | 2001 | Italy | Caucasian | Leiomyoma | HB | PCR | 35 | 57 | 27 | 119 | 46 | 77 | 33 | 156 | 0.941 | 5 |
| Suzuki | 2003 | Japan | Asian | Prostate | PB | PCR | 46 | 43 | 12 | 101 | 29 | 59 | 26 | 114 | 0.702 | 9 |
| Massart | 2003 | Italy | Caucasian | Leiomyoma | HB | PCR-RFLP | 54 | 91 | 43 | 188 | 66 | 111 | 48 | 225 | 0.917 | 5 |
| Iwamoto | 2003 | Japan | Asian | Endometrial | HB | PCR-RFLP | 25 | 54 | 13 | 92 | 25 | 28 | 12 | 65 | 0.408 | 4 |
| Shin | 2003 | Korea | Asian | Breast | PB | PCR-RFLP | 75 | 91 | 35 | 201 | 64 | 105 | 26 | 195 | 0.095 | 8 |
| Tanaka | 2003 | Japan | Asian | Prostate | HB | PCR | 23 | 63 | 29 | 115 | 39 | 113 | 48 | 200 | 0.061 | 6 |
| Cai | 2003 | China | Asian | Breast | PB | PCR-RFLP | 415 | 516 | 138 | 1069 | 430 | 546 | 190 | 1166 | 0.452 | 12 |
| Fukatsu | 2004 | Japan | Asian | Prostate | HB | PCR-RFLP | 37 | 57 | 22 | 116 | 81 | 110 | 47 | 238 | 0.384 | 6 |
| wedren | 2004 | Sweden | Caucasian | Breast | PB | PCR-RFLP | 390 | 634 | 268 | 1292 | 384 | 651 | 313 | 1348 | 0.248 | 10 |
| Lu | 2005 | China | Asian | Breast | HB | PCR-RFLP | 54 | 65 | 19 | 138 | 50 | 69 | 21 | 140 | 0.723 | 78 |
| Modugno | 2005 | USA | Caucasian | Breast | PB | PCR-RFLP | 53 | 115 | 80 | 248 | 819 | 1810 | 1272 | 3901 | 0.000 | 6 |
| Onland-Moret | 2005 | Netherlands | Caucasian | Breast | PB | PCR-RFLP | 89 | 150 | 69 | 308 | 88 | 153 | 96 | 337 | 0.093 | 9 |
| Low | 2006 | UK | Caucasian | Prostate | PB | TaqMan | 13 | 41 | 21 | 75 | 49 | 84 | 25 | 158 | 0.266 | 2 |
| Al-Hendy | 2006 | USA | African | Leiomyoma | HB | PCR-RFLP | 22 | 34 | 36 | 92 | 9 | 9 | 3 | 21 | 0.760 | 3 |
| Al-Hendy | 2006 | USA | Caucasian | Leiomyoma | HB | PCR-RFLP | 21 | 23 | 17 | 61 | 57 | 99 | 1 | 157 | 0.000 | 2 |
| Al-Hendy | 2006 | USA | Hispanic | Leiomyoma | HB | PCR-RFLP | 14 | 23 | 8 | 45 | 27 | 18 | 6 | 51 | 0.284 | 11 |
| Zhai | 2006 | China | Asian | HCC | PB | PCR-RFLP | 74 | 117 | 53 | 244 | 91 | 116 | 30 | 237 | 0.457 | 6 |
| Chen | 2006 | China | Asian | Leiomyoma | HB | PCR-RFLP | 35 | 37 | 11 | 83 | 31 | 38 | 9 | 78 | 0.604 | 5 |
| Denschlag | 2006 | Germany | Caucasian | Leiomyoma | PB | PCR | 33 | 66 | 31 | 130 | 40 | 59 | 40 | 139 | 0.075 | 9 |
| Hernandez | 2006 | USA | Caucasian | Prostate | PB | TaqMan | 47 | 55 | 18 | 120 | 129 | 131 | 43 | 303 | 0.300 | 11 |
| Hernandez | 2006 | USA | Caucasian | Prostate | PB | TaqMan | 115 | 216 | 100 | 431 | 154 | 296 | 132 | 582 | 0.653 | 9 |
| Hernandez | 2006 | USA | African | Prostate | PB | TaqMan | 9 | 22 | 16 | 47 | 50 | 113 | 50 | 213 | 0.373 | 11 |
| Shen | 2006 | China | Asian | Breast | PB | PCR-RFLP | 98 | 120 | 29 | 247 | 107 | 124 | 43 | 274 | 0.480 | 10 |
| Cunningham | 2007 | Minnesota | Caucasian | Prostate | PB | PCR | 257 | 454 | 213 | 924 | 120 | 249 | 120 | 489 | 0.684 | 9 |
| Berndt | 2007 | USA | Caucasian | Prostate | HB | PCR | 121 | 238 | 111 | 470 | 152 | 316 | 135 | 603 | 0.230 | 9 |
| Hsieh | 2007 | China | Asian | Leiomyoma | PB | PCR-RFLP | 25 | 75 | 6 | 106 | 60 | 44 | 6 | 110 | 0.571 | 7 |
| Hu | 2007 | China | Asian | Breast | HB | PCR-RFLP | 39 | 58 | 16 | 113 | 49 | 45 | 19 | 113 | 0.128 | 7 |
| Kadiyska | 2007 | Bulgaria | Caucasian | Colorectal | HB | PCR-RFLP | 34 | 79 | 27 | 140 | 23 | 35 | 19 | 77 | 0.438 | 11 |
| Kjaergaard | 2007 | Danmark | Caucasian | Prostate | PB | TaqMan | 35 | 55 | 26 | 116 | 1203 | 1972 | 830 | 4005 | 0.676 | 11 |
| Kjaergaard | 2007 | Danmark | Caucasian | Breast | PB | TaqMan | 398 | 613 | 245 | 1256 | 727 | 1225 | 537 | 2489 | 0.621 | 7 |
| Wang | 2007 | USA | Caucasian | Breast | PB | PCR | 117 | 188 | 87 | 392 | 214 | 393 | 176 | 783 | 0.862 | 4 |
| Onsory | 2008 | India | Asian | Prostate | HB | PCR-RFLP | 28 | 54 | 18 | 100 | 42 | 48 | 10 | 100 | 0.487 | |
| González-Mancha | 2008 | Spain | Caucasian | Breast | PB | PCR-RFLP | 153 | 209 | 82 | 444 | 193 | 361 | 150 | 704 | 0.435 | 6 |
| Sobti | 2008 | India | Asian | Prostate | HB | PCR | 52 | 77 | 28 | 157 | 64 | 90 | 16 | 170 | 0.050 | 6 |
| Gonzalez-Zuloeta | 2008 | Netherlands | Caucasian | Breast | PB | PCR-RFLP | 72 | 94 | 24 | 190 | 1602 | 1648 | 453 | 3703 | 0.359 | 6 |
| Dunning | 2009 | UK | Caucasian | Breast | PB | TaqMan | 1260 | 2164 | 938 | 4362 | 1318 | 2296 | 934 | 4548 | 0.253 | 8 |
| Ashton | 2009 | Australia | Caucasian | Endometrial | PB | PCR-RLFP | 39 | 95 | 57 | 191 | 96 | 129 | 65 | 290 | 0.088 | 11 |
| Iwasaki | 2009 | Japan | Asian | Breast | HB | TaqMan | 144 | 180 | 64 | 388 | 115 | 196 | 77 | 388 | 0.692 | 10 |
| Iwasaki | 2009 | Japan | Asian | Breast | HB | TaqMan | 25 | 39 | 15 | 79 | 22 | 43 | 14 | 79 | 0.374 | 9 |
| Iwasaki | 2009 | Japan | Asian | Breast | HB | TaqMan | 107 | 187 | 85 | 379 | 122 | 194 | 63 | 379 | 0.338 | 10 |

| Surname | Year | Country | Ethnicity | Cancer type | Control Source | Genotype method | Case | | | | Control | | | | HWE | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | TT | CT | CC | All | TT | CT | CC | All | | |
| Sonestedt | 2009 | Sweden | Caucasian | Breast | PB | MassARRAY | 158 | 273 | 108 | 539 | 316 | 539 | 218 | 1073 | 0.667 | 10 |
| Beuten | 2009 | USA | non-Hispanic Caucasians | Prostate | PB | PCR | 167 | 304 | 138 | 609 | 222 | 421 | 200 | 843 | 0.988 | 7 |
| Beuten | 2009 | USA | Hispanic Caucasians | Prostate | PB | PCR | 75 | 92 | 28 | 195 | 186 | 246 | 82 | 514 | 0.964 | 7 |
| Beuten | 2009 | USA | African | Prostate | PB | PCR | 18 | 41 | 23 | 82 | 54 | 105 | 50 | 209 | 0.940 | 7 |
| Anghel | 2009 | Romania | Caucasian | Bladder | HB | PCR | 0 | 6 | 9 | 15 | 18 | 48 | 48 | 114 | 0.309 | 5 |
| Anghel | 2009 | Romania | Caucasian | Colorectal | HB | PCR | 2 | 13 | 3 | 18 | 18 | 48 | 48 | 114 | 0.309 | 5 |
| Anghel | 2009 | Romania | Caucasian | AML | HB | PCR | 0 | 5 | 10 | 15 | 18 | 48 | 48 | 114 | 0.309 | 5 |
| Anghel | 2009 | Romania | Caucasian | HCC | HB | PCR | 2 | 6 | 4 | 12 | 18 | 48 | 48 | 114 | 0.309 | 5 |
| Anghel | 2009 | Romania | Caucasian | Breast | HB | PCR | 4 | 65 | 32 | 101 | 15 | 38 | 37 | 90 | 0.333 | 6 |
| Wang JY | 2010 | China | Asian | Leiomyoma | HB | PCR-RFLP | 24 | 46 | 22 | 92 | 51 | 100 | 42 | 193 | 0.592 | 6 |
| Wang XL | 2010 | China | Asian | Leiomyoma | HB | PCR-RFLP | 42 | 48 | 12 | 102 | 35 | 49 | 16 | 100 | 0.867 | 6 |
| Gupta | 2010 | India | Asian | Prostate | HB | PCR-RFLP | 52 | 77 | 28 | 157 | 64 | 90 | 16 | 170 | 0.049 | 6 |
| Park | 2010 | China | Asian | Gallbladder | PB | PCR-RFLP | 41 | 100 | 94 | 235 | 108 | 356 | 314 | 778 | 0.658 | 11 |
| Sonoda | 2010 | Japan | Asian | Prostate | HB | PCR | 60 | 89 | 31 | 180 | 61 | 87 | 29 | 177 | 0.828 | 5 |
| Sakoda | 2011 | China | Asian | Breast | PB | PCR | 229 | 290 | 93 | 612 | 327 | 427 | 120 | 874 | 0.298 | 12 |
| Deng | 2011 | China | Asian | Breast | HB | PCR-RFLP | 42 | 63 | 23 | 128 | 52 | 61 | 17 | 130 | 0.892 | 7 |
| Wang | 2011 | China | Asian | Cervical | HB | PCR-RFLP | 39 | 45 | 18 | 102 | 32 | 52 | 18 | 102 | 0.692 | 6 |
| Sissung | 2011 | USA | Caucasian | Prostate | PB | TaqMan | 25 | 75 | 28 | 128 | 46 | 60 | 20 | 126 | 0.952 | 3 |
| de Giorgi | 2011 | Italy | Caucasian | Melanoma | HB | PCR-RFLP | 32 | 49 | 31 | 112 | 56 | 98 | 41 | 195 | 0.876 | 6 |
| Balistreri | 2011 | Italy | Caucasian | Prostate | HB | PCR-RFLP | 37 | 11 | 2 | 50 | 84 | 7 | 0 | 91 | 0.702 | 4 |
| Han | 2011 | China | Asian | Breast | PB | TaqMan | 353 | 399 | 107 | 859 | 324 | 402 | 151 | 877 | 0.171 | 9 |
| Szendroi | 2011 | Hungary | Caucasian | Prostate | HB | PCR-RFLP | 43 | 122 | 39 | 204 | 31 | 47 | 25 | 103 | 0.392 | 7 |
| Lundie | 2012 | USA | Caucasian | Endometrial | PB | PCR | 116 | 184 | 91 | 391 | 194 | 369 | 146 | 709 | 0.223 | 9 |
| Srivastava | 2012 | India | Asian | Gallbladder | PB | PCR-RFLP | 59 | 218 | 133 | 410 | 19 | 110 | 91 | 220 | 0.075 | 12 |
| Safarinejad | 2012 | Iran | Asian | Prostate | PB | PCR-RFLP | 11 | 94 | 57 | 162 | 65 | 169 | 90 | 324 | 0.373 | 6 |
| Chang | 2012 | China | Asian | Lung | HB | PCR-RFLP | 21 | 60 | 3 | 84 | 62 | 132 | 40 | 234 | 0.034 | 4 |
| Tang | 2013 | China | Asian | Breast | HB | MALDI-TOF | 293 | 374 | 127 | 794 | 334 | 375 | 136 | 845 | 0.076 | 9 |
| Jurecekova | 2013 | Slovak | Caucasian | Prostate | HB | PCR | 78 | 154 | 79 | 311 | 81 | 126 | 49 | 256 | 1 | 5 |
| Pazarbasi | 2013 | Turkey | Caucasian | Prostate | HB | PCR | 14 | 14 | 6 | 34 | 10 | 7 | 10 | 27 | 0.012 | 3 |
| Ramalhinho | 2013 | Portugal | Caucasian | Breast | HB | PCR-RFLP | 28 | 60 | 19 | 107 | 45 | 60 | 16 | 121 | 0.566 | 7 |
| Liu | 2014 | China | Asian | HCC | HB | PCR | 34 | 54 | 19 | 107 | 57 | 38 | 10 | 105 | 0.331 | 6 |
| Chattopadhyay | 2014 | India | Asian | Breast | PB | PCR-RFLP | 157 | 164 | 39 | 360 | 136 | 162 | 62 | 360 | 0.252 | 11 |
| Lu | 2014 | China | Asian | Breast | HB | PCR-RFLP | 227 | 258 | 57 | 542 | 425 | 454 | 137 | 1016 | 0.368 | 5 |
| Madeira | 2014 | Brazil | Asian | Breast | HB | PCR-RFLP | 6 | 49 | 9 | 64 | 25 | 39 | 8 | 72 | 0.211 | 6 |
| Taghizade | 2014 | Iran | Asian | Leiomyoma | HB | PCR-RFLP | 78 | 133 | 65 | 276 | 50 | 74 | 33 | 157 | 0.563 | 7 |
| Cao | 2014 | China | Asian | Breast | HB | PCR-RFLP | 70 | 109 | 42 | 221 | 79 | 124 | 49 | 252 | 0.978 | 7 |
| Lu | 2015 | Japan | Asian | Prostate | HB | TaqMan | 67 | 191 | 94 | 352 | 80 | 175 | 97 | 352 | 0.949 | 7 |
| Nyante | 2015 | USA | Caucasian | Breast | PB | PCR | 518 | 984 | 470 | 1972 | 469 | 908 | 398 | 1775 | 0.297 | 11 |
| Han | 2017 | China | Asian | Prostate | HB | PCR | 94 | 102 | 48 | 244 | 92 | 112 | 28 | 232 | 0.492 | 8 |

**Abbreviations:** HB, hospital based; PB, population based; PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; HCC, hepatocarcinoma; AML, acute myeloid leukemia; HWE, Hardy-Weinberg equilibrium.

## Meta-analysis results

The summary results of meta-analysis were presented in **Table 2** and **Figure 2**. In all, no significant association between the *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk was observed under homozygous model (TT vs. CC: OR=0.92, 95% CI=0.84-1.01) and heterozygous model (TT vs. CT: OR=0.94, 95% CI=0.88-1.001). Statistically significant relationship was only observed for PvuII in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99).

In subgroup analysis by cancer type, we found that the T genotype significantly decreased prostate cancer risk (TT vs. CC: OR=0.79, 95% CI=0.66-0.94; T vs. C: OR=0.89, 95% CI=0.82-0.98), Leiomyoma risk (T vs. C: OR=0.82, 95% CI=0.68-0.98), and HCC risk (TT vs. CC: OR=0.45, 95% CI=0.28-0.71; T vs. C: OR=0.67, 95% CI=0.47-0.95). However, no relationship between *ESR1* PvuII polymorphism and any other types of cancer was observed. Ethnicity subgroup analysis revealed that significant association between *ESR1* PvuII genotype and cancer risk was detected among African (TT vs. CC: OR=0.54, 95% CI=0.30-0.98), and Hispanics (TT vs. CT: OR=0.41, 95% CI=0.17-0.99; T vs. C: OR=0.55, 95% CI=0.30-0.99). Such association was not observed for the Asians and Caucasians. In terms of source of controls, we found that the *ESR1* PvuII T genotype help to decrease cancer risk in hospital-based group (T vs. C: OR=0.89, 95% CI=0.83-0.96) and in population-based group (TT vs. CC: OR=0.81, 95% CI=0.70-0.94; TT vs. CT: OR=0.86, 95% CI=0.78-0.96). Further subgroup analysis by HWE in controls also failed to detect positive association, except for heterogenous model in HWE>0.05 subgroup (TT vs. CT: OR=0.94, 95% CI=0.88-1.00). Subgroup analysis of quality revealed that *ESR1* PvuII T genotype help to decrease cancer risk in group with quality score ≤9.

## Heterogeneity and sensitivity analysis

Between-study heterogeneity was first calculated by using $Q$ test and $I^2$ statistics. We used the random-effect model as significant heterogeneity was observed among all three genetic models ($P$<0.001) in the pooled analysis (TT vs. CC: $P$<0.001, $I^2$ = 59.1%; TT vs. CT: $P$<0.001, $I^2$ = 49.4%; T vs. C:

*P*<0.001, $I^2$ = 61.0%). In addition, sequential leave-one-out sensitivity analysis was adopted to evaluate the stability of the results. After removing each study, no substantial changes in pooled results were found (**Figure 3**).

### Publication bias

The shape of Begg's funnel plots was quite symmetry (**Figure 4**). Moreover, statistical evidence of Egger's test also provided the none-existence of publication bias among the studies (data not shown).

## Discussion

In this meta-analysis, we comprehensively evaluated the association between *ESR1* PvuII (rs2234693 T>C) polymorphism with cancer susceptibility. The obtained results suggested *ESR1* PvuII (rs2234693 T>C) polymorphism may influence overall cancer risk in a low impact effect manner. So far, this meta-analysis represents the most powerful investigation in elucidating the role of *ESR1* PvuII (rs2234693 T>C) in cancer risk.

The polymorphism of *ESR1,* PvuII (rs2234693 T>C), can affect *ESR1* transcription activity and further contribute to the carcinogenesis. A myriad of studies has investigated the role of *ESR1* PvuII (rs2234693 T>C) polymorphisms in cancer risk. In 2001, Massart et al. claimed that the PvuII and XbaI polymorphisms in the *ESR1* gene do not produce different risks of developing uterine leiomyomas [52]. In another study performed in urban Shanghai with 1069 breast cancer patients and 1166 controls, Cai et al. found that *ESR1* PvuII (rs2234693 T>C) polymorphism conferred to an enhanced risk of breast cancer among subjects carrying Pp (CT) and pp (TT) genotypes [21]. Yet, AI-Hendy et al. claimed that the *ESR1*PvuII PP (CC) genotype contributed to a significantly increased risk of uterine leiomyomas in black and white women, but not in Hispanic women [15]. Many meta-analyses have been conducted aiming to obtain a clear association between *ESR1* PvuII (rs2234693 T>C) and cancer risk. In 2010, Li et al. performed a meta-analysis regarding the association of several potentially functional SNPs in *ESR1* with breast cancer risk. This analysis on 10,300 breast cancer cases and 16,620 controls in PvuII (rs2234693 T>C) polymorphism revealed a borderline significant decreased breast cancer risk for CC and CC/CT carriers (CC vs. TT: OR=0.92, 95% CI=0.86-0.99; CC/CT vs. TT: OR=0.95, 95% CI=0.89-1.00) [84]. In a meta-analysis updated to April 2014, 41 studies were included to analyze the relationship between *ESR1* PvuII (rs2234693 T>C) and cancer risk. Results of the pooled analysis suggested a null relationship between PvuII (rs2234693 T>C) polymorphism and overall cancer risk. Subgroup analysis indicated that PvuII (rs2234693 T>C) polymorphism was associated with a decreased risk of gallbladder cancer, in contrast with the increased risk of prostate cancer and hepatocellular carcinoma (HCC). They also failed to observe significant association in Asian and Caucasian populations [85].

**Table 2.** Meta-analysis of the association between *ESR1* Pvull polymorphism and cancer risk

| Variables | No. of studies | Homozygous | | Heterozygous | | Allele | |
|---|---|---|---|---|---|---|---|
| | | TT vs. CC | | TT vs. CT | | T vs. C | |
| | | OR (95% CI) | P het | OR (95% CI) | P het | OR (95% CI) | P het |
| All | 80 | 0.92 (0.84-1.01) | <0.001 | 0.94 (0.88-1.001) | <0.001 | **0.95 (0.91-0.99)** | <0.001 |
| Cancer type | | | | | | | |
| Breast | 28 | 1.08 (0.98-1.19) | 0.001 | 1.01 (0.94-1.08) | 0.015 | 1.03 (0.99-1.08) | 0.004 |
| Prostate | 26 | **0.79 (0.66-0.94)** | <0.001 | 0.89 (0.78-1.01) | 0.006 | **0.89 (0.82-0.98)** | <0.001 |
| Leiomyoma | 11 | 0.72 (0.49-1.06) | 0.016 | 0.83 (0.61-1.12) | 0.003 | **0.82 (0.68-0.98)** | 0.006 |
| HCC | 3 | **0.45 (0.28-0.71)** | 0.353 | 0.63 (0.39-1.04) | 0.191 | **0.67 (0.47-0.95)** | 0.145 |
| Endometrial | 3 | 0.73 (0.43-1.24) | 0.067 | 0.73 (0.40-1.35) | 0.005 | 0.84 (0.63-1.11) | 0.046 |
| Others | 9 | 1.26 (0.85-1.90) | 0.070 | 1.06 (0.88-1.40) | 0.203 | 1.06 (0.88-1.28) | 0.042 |
| Ethnicity | | | | | | | |
| Asian | 38 | 0.94 (0.80-1.10) | <0.001 | 0.93 (0.84-1.04) | <0.001 | 0.96 (0.89-1.03) | <0.001 |
| Caucasian | 36 | 0.93 (0.83-1.04) | <0.001 | 0.95 (0.88-1.04) | 0.003 | 0.96 (0.90-1.01) | <0.001 |
| African | 3 | **0.54 (0.30-0.98)** | 0.292 | 0.83 (0.52-1.32) | 0.870 | 0.70 (0.49-1.001) | 0.185 |
| Hispanics | 1 | 0.39 (0.11-1.34) | - | **0.41 (0.17-0.99)** | - | **0.55 (0.30-0.99)** | - |
| Non-Hispanic Caucasian | 1 | 1.09 (0.81-1.47) | - | 1.04 (0.81-1.34) | - | 1.04 (0.90-1.21) | - |
| Hispanic Caucasian | 1 | 1.18 (0.71-1.96) | - | 1.08 (0.75-1.55) | - | 1.08 (0.85-1.38) | - |
| Control source | | | | | | | |
| HB | 44 | 1.02 (0.91-1.13) | <0.001 | 0.99 (0.92-1.08) | 0.009 | **0.89 (0.83-0.96)** | <0.001 |
| PB | 36 | **0.81 (0.70-0.94)** | <0.001 | **0.86 (0.78-0.96)** | <0.001 | 0.99 (0.95-1.05) | <0.001 |
| HWE | | | | | | | |
| >0.05 | 74 | 0.94 (0.86-1.02) | <0.001 | **0.94 (0.88-1.00)** | <0.001 | 0.96 (0.92-1.001) | <0.001 |
| ≤0.05 | 6 | 0.74 (0.33-1.67) | <0.001 | 0.98 (0.80-1.21) | 0.672 | 0.90 (0.70-1.14) | 0.009 |
| Quality score | | | | | | | |
| >9 | 17 | 1.07 (0.92-1.23) | 0.386 | 1.04 (0.98-1.11) | 0.327 | 1.03 (0.96-1.10) | <0.001 |
| ≤9 | 63 | **0.86 (0.77-0.96)** | 0.008 | **0.88 (0.81-0.96)** | <0.001 | **0.92 (0.87-0.97)** | <0.001 |

**Abbreviations:** Het, heterogeneity; HB, hospital based; PB, population based.

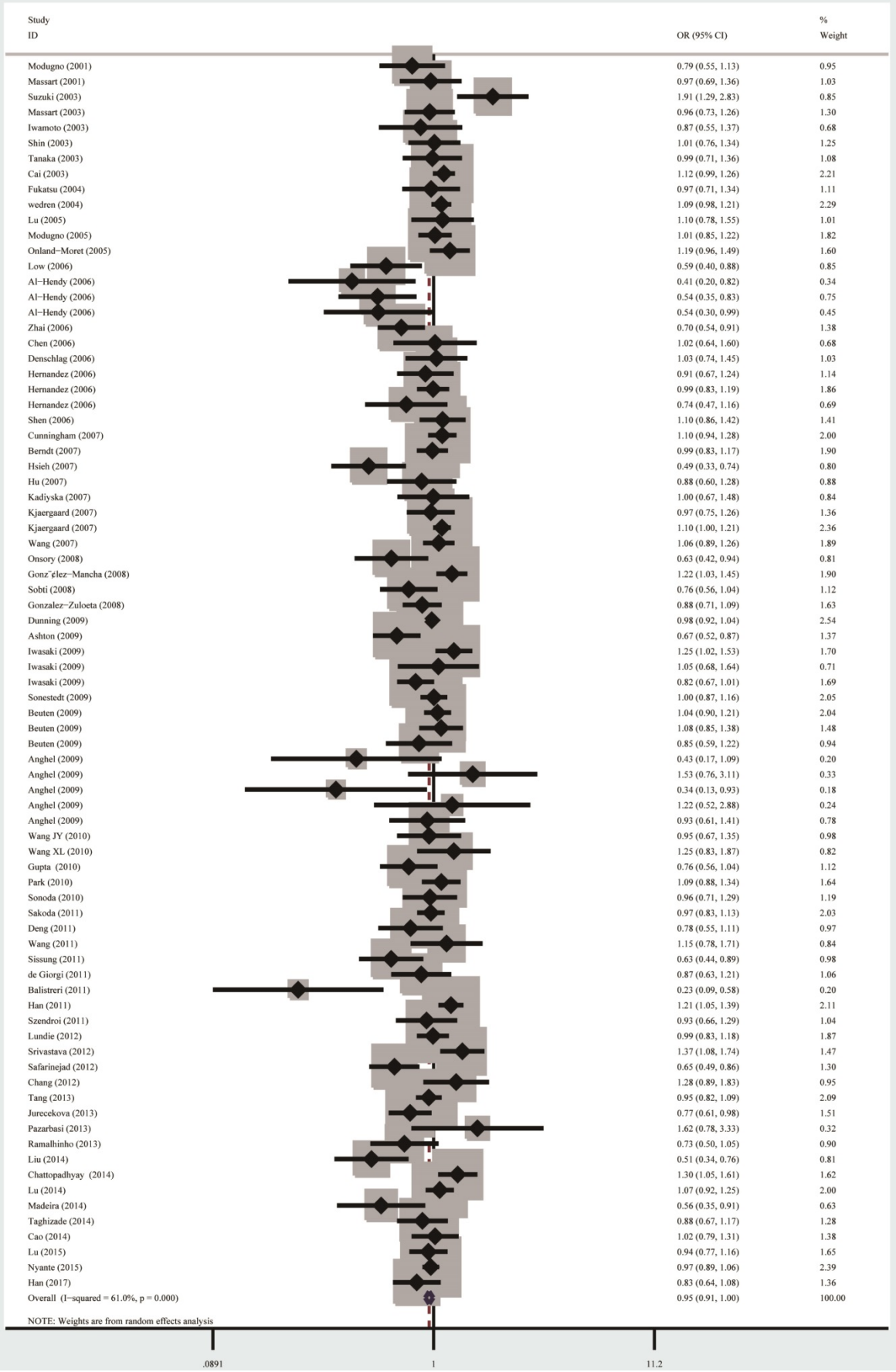


**Figure 2.** Forest plot for the overall cancer susceptibility associated with the *ESR1* PvuII (T>C) polymorphism under allele comparison model. **Notes:** The horizontal lines represent the study-specific ORs and 95% CIs, respectively. The diamond represents the pooled results of OR and 95% CI.

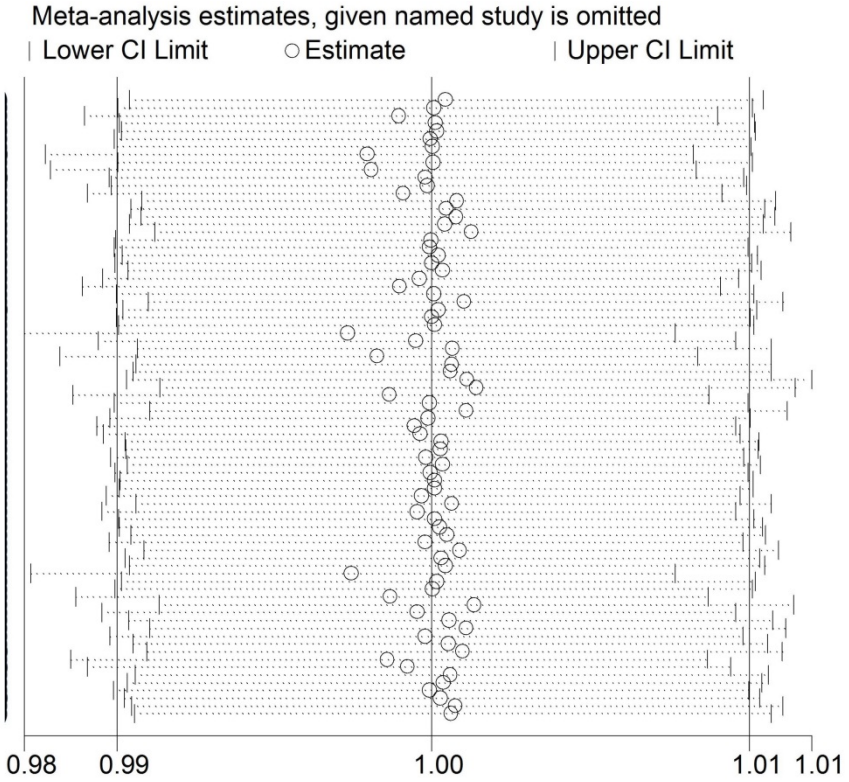


**Figure 3.** Sensitivity analysis of the association between *ESR1* PvuII (T>C) polymorphism and cancer susceptibility. Each point represents the recalculated OR after deleting a separate study.

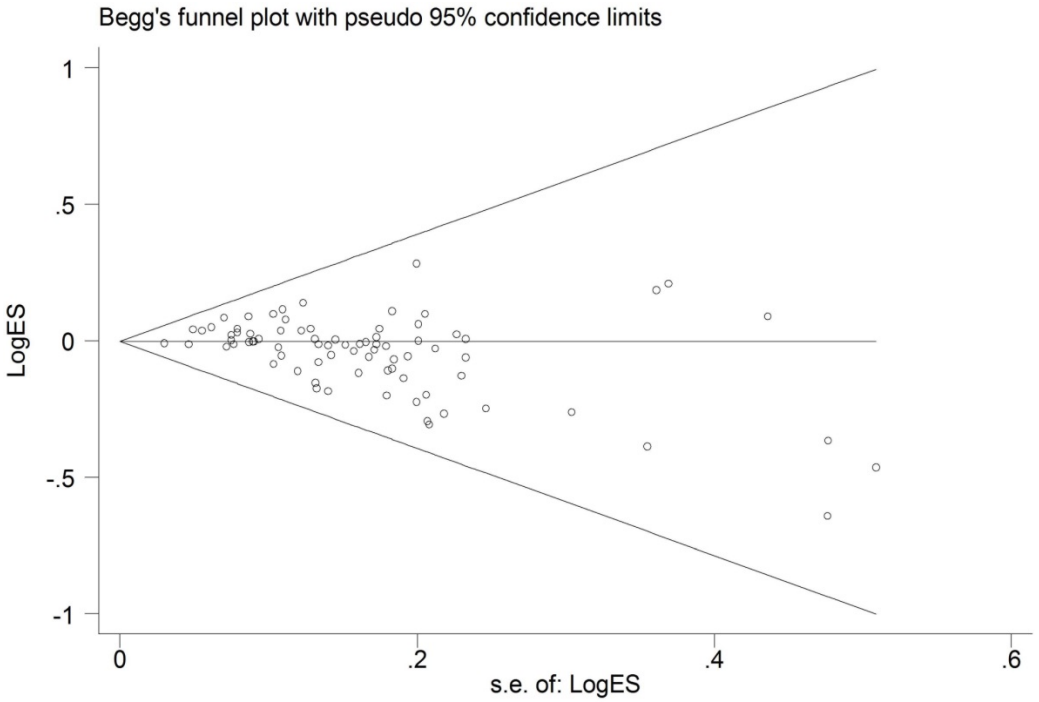


**Figure 4.** Funnel plot analysis to detect publication bias for *ESR1* PvuII (T>C) polymorphism under allele comparison model. **Notes:** Each point represents a separate study for the indicated association.

From then on, several new case-control studies with larger samples were available. In addition, the former meta-analysis conducted only included studies published in English. To provide a robust clarification, we performed the updated meta-analysis by involving all the eligible studies published. Overall, statistically significant relationship was only observed for PvuII in allele model T vs. C (OR=0.95, 95% CI=0.91-0.99). However, we did not detect any significant relationship between *ESR1* PvuII

(rs2234693 T>C) polymorphism and cancer risk in the pooled analysis under homozygous and heterozygous model. Cancer type by subgroup analysis indicated that T genotype significantly decreased prostate cancer risk, Leiomyoma risk, and HCC risk. Yet no association was observed in other types of cancers. These data suggested that the PvuII (rs2234693 T>C) polymorphism on *ESR1* may function in a wide manner regarding the different cancer types. When stratified by population, no significant association between *ESR1* PvuII genotype and cancer risk among African, and Hispanics was detected. Such association was observed for the Africans. The limited statistical power caused by relatively small number of studies in Africans should be considered.

In this meta-analysis, several measurements were performed to enhance the credibility of our conclusion. First, we adopted every effort to expand the numbers of included studies, such as incorporating all publications written both in Chinese and in English. The relatively large number of including studies was one of the important merits of the current study. We also performed publication bias and the sensitivity analysis under the guidance of Cochrane protocol. The sensitivity analysis and publication bias analysis revealed the strength of our conclusions. Although this meta-analysis has its own merits, limitations still exist. First, we only used unadjusted estimates to determine whether there is a relationship between *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer risk. Adjustment analysis was absence due to the lack of patient's clinical data such as life habit, smoking and drinking status, exposing factors, and gene-environment interactions, which restrains our further analysis for confounding factors. Second, the validity of conclusion was impaired as significant between-study heterogeneity was detected in some comparisons. Such heterogeneity might result from different quality of studies, and might impair the strength of the conclusion. Third, selection bias and language bias were inevitable, as only published studies and papers written in English or Chinese were analyzed, respectively. Moreover, selection bias might also generate as most of the studies included in this meta-analysis were from candidate gene based, but not from GWAS. Fourth, the sample size of subgroup analysis was relatively small in some strata, impaired the statistical power to estimate the real association. Last, the analyzed case-control studies were mostly performed using Caucasians and Asians populations. Therefore, more trials using different population background, especially Africans, are essential to further confirm such conclusion, due to the genetic and geographical differences.

## Conclusion

In conclusion, the current meta-analysis suggests that *ESR1* PvuII (rs2234693 T>C) polymorphism may not be strong enough to impact the risk of cancer, based on the pooled results of the published articles. Such relationship further helps to explain the etiology of cancer. Yet, further epidemiological studies with larger sample sizes, standardized unbiased design are warranted to confirm this conclusion.

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## Competing Interests

The authors have declared that no competing interest exists.

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