## **RESEARCH COMMUNICATION**

# **XRCC1 Arg399Gln Gene Polymorphism and Breast Cancer Risk: a Meta-analysis Based on Case-control Studies**

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#### Abstract

Background: The Arg399Gln polymorphism in the XRCC1 DNA repair gene is likely to be involved with the development of breast cancer (BC). However, there have been inconsistent reports of association. The objective of this study was to systematically evaluate the published papers. Methods: We performed a meta-analysis of 44 published case-control studies fitting our eligibility criteria. These studies involved XRCC1 Arg399Gln polymorphisms in 20,841 BC cases and 22,688 controls in dominant (GlnGln+ArgGln vs. ArgArg), recessive (GlnGln vs. ArgGln+ArgArg), and co-dominant (GlnGln vs. ArgArg) inheritance models. Analyses of Asian, African and Caucasian ethnic subgroups was also conducted. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations. <u>Results</u>: Our overall analyses indicated Arg399Gln to be associated with a trend of increased BC risk when using recessive (OR=1.15, 95% CI: 1.05-1.27), and co-dominant models (OR=1.15, 95% CI: 1.04-1.27) to analyze the data. In ethnic subgroups, Arg399Gln significantly increased BC risk in Asians (OR=1.54, 95% CI: 1.18–2.01) when using recessive model analysis, in Africans (OR=1.30, 95% CI: 1.07–1.60) when using dominant model analysis, and in Asians (OR=1.50, 95% CI: 1.15–1.97) and Africans (OR=1.80, 95% CI: 1.08-3.02) when using the co-dominant model analysis. Conclusions: From our meta-analysis of data from 44 publications, we conclude that XRCC1 Arg399Gln allele is a risk factor for the development breast cancer, especially among Asian and African populations.

Key words: XRCC1 gene polymorphism - Arg399Gln - breast cancer

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## Introduction

Genetic variation in DNA repair genes can cause alteration in DNA repair function, resulting in the accumulation of DNA damage and gene mutations, and the development of health consequences such as cancer (Harms et al., 2004). Base-excision repair (BER) is an important DNA repair pathway that is responsible for the repair of base damage resulting from exposure to X-rays, oxygen radicals, and alkylating agents (Goode et al., 2002; Hoeijmakers, 2001; Wood et al., 2001). The X-ray repair cross-complementing group 1 gene (XRCC1) is one of these DNA repair genes in the pathway. XRCC1 acts as a central scaffolding protein by binding to DNA ligase III, DNA polymerase  $\beta$ , and poly (ADP-ribose) polymerase in BER at the site of damaged DNA (Cappelli et al., 1997; Masson et al., 1998). Like most genes, XRCC1has numerous genetic variations (Goode et al., 2002). These variations, such as Arg399Gln, can alter the DNA repair function of the gene and therefore health outcomes (Duell et al., 2002).

Case-control study is a well-accepted method to investigate the association between diseases and specific genes, e.g. XRCC1 Arg399Gln polymorphism and BC. However, previous studies regarding the relationships have provided inconsistent results. For example, Saadat et al. (2008) reported that 399Gln allele acted as a recessive allele and increased the BC risk (Gln/Gln vs. Arg/Arg+Arg/Gln, OR=2.31, 95%CI: 1.21-4.35). However, Costa et al. (2007) reported that women with XRCC1 399Gln genotypes were protected against BC (OR=0.54, 95%= CI: 0.35-0.84). It has also been suggested that the relationship between XRCC1 Arg399Gln and BC risk might be modified by ethnicity of the population and/or family history (Li et al., 2009). Among other studies Thyagarajan et al. (2006) concluded that there was no significant association between BC and the polymorphism.

There can be many reasons for the discrepancy in the publications. One is the small sample sizes of cases and controls. The other is the complication by the use and comparison of different ethnic populations. So, a

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systematic meta-analysis of the available studies can provide more definitive answers. In addition, with the much larger sample size from the combined reports, the impact from ethnicity and other factors can be better elucidated. Therefore, we have performed such a metaanalysis on XRCC1 Arg399Gln polymorphism and BC.

## **Materials and Methods**

## Search strategy

All the case-control studies were identified by literature searches in the PubMed, CNKI, SpringerLink, Ovid, EBSCO and ScienceDirect database (prior to February 2011) using the following words and terms: 'XRCC1', 'polymorphism', 'Arg399Gln' and 'breast cancer'. References of the retrieved publications were also screened. Only research articles were included and the language of publication was restricted to English and Chinese. Studies had to be based on an unrelated case-control design, so pedigree data were excluded. The genotype distribution of the control population of the studies had to be in Hardy-Weinberg equilibrium (HWE) (P>0.05). All selected studies had to fulfill the following four criteria: (1) case-control study of the Arg399Gln polymorphism and breast cancer risk; (2) sufficient published data for estimating an odds ratio with 95% confidence interval; (3) when multiple publications reported on the same or overlapping data, we selected the largest or most recent publication, as recommended by Little et al. (2002) and (4) clear description of ethnic background of study populations.

### Data extraction

The information was extracted from each publication: the first author's name, journals or publication data, year of publications, country origin, sources of controls, ethnic descent of the study population (categorized as Asian, Caucasian, and African), genotyping method, and number of different genotype in all subjects.

#### Statistical analysis

We examined the association between Arg399Gln polymorphism and the risk of BC, using codominant (Gln/Gln versus Arg/Arg), recessive (Gln/Gln versus Arg/Gln+Arg/Arg) and dominant (GlnGln+ArgGln versus ArgArg) genetic models. In our study, both Mantel-Haenszel's fixed-effects method and DerSimonian and Laird's random-effects method were used. A chi-square based Q test and an I2 test were both performed to evaluate the between-study heterogeneity of the studies. Venice criteria (Ioannidis et al., 2008) for the I<sup>2</sup> test included: 'I<sup>2</sup> < 25% represents no heterogeneity,  $I^2 = 25-50\%$  represents moderate heterogeneity,  $I^2 =$ 50-75% represents large heterogeneity and I2>75% represents extreme heterogeneity'. So in this study if P <0.10 or  $I^2 > 25\%$ , the between-study heterogeneity was therefore considered to be significant, we chose the random-effects model to calculate the OR. If not, the fixed effects model was performed. RevMan 5.0 software was employed to estimate summary OR and 95% CI by weighting each study result by a factor of within- and between-study variance. A Z test was performed to determine the significance of the pooled OR. For each genetic comparison, subgroup analysis was performed according to ethnic descent status: Asian, African or Caucasian. Funnel plots were used to access publication bias by the method of Begg's test (Begg and Mazumdar, 1994) and Egger's test (Egger et al., 1997). An asymmetric plot suggested possible publication bias (P ≥0.05 suggests no bias). Hardy-Weinberg equilibrium was tested by the chi-square test based on an Excel programme. Analyses were performed by SPSS 15.0 for Windows (SPSS Inc.) and RevMan 5.0 software.

## **Results**

## Study characteristics

There were 40 publications based on casecontrol studies that met the inclusion criteria (Listed alphabetically: Ali et al., 2008; BCAC, 2006; Brewster et al., 2006; Bu et al., 2006; Chacko et al., 2005; Costa et al., 2007; Deligezer and Dalay, 2004; Duell et al., 2001; Dufloth et al., 2005; Figueiredo et al., 2004; Forsti et al., 2004; Han et al., 2003; Hsu et al., 2010; Hussien et al., 2011; Jelonek et al., 2010; Jin et al., 2006; Kim et al., 2002; Kipikasova et al., 2008; Liu et al., 2011; Loizidou et al., 2008; Metsola et al., 2005; Mitra et al., 2008; Moullan et al., 2003; Pachkowski et al., 2006; Patel et al., 2005; Saadat et al., 2008; Sangrajrang et al., 2008; Santos et al., 2010; Shen et al., 2005; Shu et al., 2003; Silva et al., 2007; Smith et al., 2008; Smith et al., 2003a; Smith et al., 2003b; Sterpone et al., 2010; Syamala et al., 2009; Thyagarajan et al., 2006; Zhai et al., 2006; Zhang et al., 2006; Zipprich et al., 2010). Each subpopulation in these articles was treated as a separate study in our meta-analysis. One combined analysis (BCAC, 2006) included nine individual casecontrol studies, two of which (studies PBSC and US 3-state) were also reported by Zhang et al. (2006) with more cases being included. Thus, our meta-analysis started with 49 studies from 40 publications (Table 1). We extracted the eligible data and rejected data where HWE was doubtful. Five studies were not in agreement with the equilibrium of the Arg399Gln in the controls (Table 1), for this reason they were not included in the final meta-analysis. As a result, 44 case-control studies including 20 841 cases and 22 688 controls for Arg399Gln polymorphism were identified for this meta-analysis. Populations were divided into three ethnic categories: Caucasian, Asian, and African.

#### Meta-analysis result of Arg399Gln and breast cancer

A summary of our results is shown in Table 2. For each study, we investigated the association based on the assumption of different inheritance models of the

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| First author | r Year Country |           | Ethnicity | Control source |        | Case   |        |        | in controls† |        |          |
|--------------|----------------|-----------|-----------|----------------|--------|--------|--------|--------|--------------|--------|----------|
|              |                |           |           |                | ArgArg | ArgGln | GlnGln | ArgArg | ArgGln       | GlnGln |          |
| Duell        | 2001           | USA       | African   | Population     | 164    | 82     | 7      | 198    | 64           | 4      | 0.221    |
| Duell        | 2001           | USA       | Caucasian | Population     | 162    | 175    | 49     | 164    | 158          | 59     | 3.998*   |
| Kim          | 2002           | Korea     | Korean    | Hospital       | 92     | 79     | 34     | 90     | 101          | 14     | 4.156*   |
| Shu          | 2003           | China     | Chinese   | Population     | 561    | 442    | 85     | 610    | 498          | 74     | 4.365*   |
| Smith        | 2003a          | USA       | Caucasian | Hospital       | 99     | 122    | 30     | 115    | 123          | 29     | 0.207    |
| Moullan      | 2003           | France    | French    | Population     | 109    | 113    | 32     | 127    | 146          | 39     | 0.087    |
| Smith        | 2003b          | USA       | Caucasian | Hospital       | 70     | 72     | 20     | 119    | 150          | 31     | 2.659    |
| Han          | 2003           | USA       | Caucasian | Population     | 391    | 460    | 135    | 545    | 616          | 176    | 0.009    |
| Deligezer    | 2004           | Turkey    | Turkish   | Unknown        | 58     | 68     | 25     | 50     | 66           | 17     | 0.442    |
| Figueiredo   | 2004           | Canada    | Caucasian | Population     | 168    | 179    | 55     | 160    | 185          | 57     | 0.089    |
| Forsti       | 2004           | Finland   | Finnish   | Population     | 100    | 103    | 20     | 138    | 129          | 31     | 0.011    |
| Dufloth      | 2005           | Brazil    | Brazilian | Population     | 46     | 33     | 7      | 118    | 100          | 20     | 0.017    |
| Patel        | 2005           | USA       | Caucasian | Population     | 196    | 195    | 61     | 280    | 202          | 56     | 0.092    |
| Chacko       | 2005           | India     | Indian    | Hospital       | 56     | 50     | 17     | 79     | 35           | 9      | 3.081    |
| Shen         | 2005           | USA       | Caucasian | Population     | 412    | 539    | 116    | 444    | 536          | 130    | 2.75     |
| Metsola      | 2005           | Finland   | Finnish   | Hospital       | 237    | 196    | 46     | 256    | 185          | 37     | 0.193    |
| Thyagarajan  | 2006           | USA       | Caucasian | Population     | 57     | 76     | 60     | 135    | 140          | 47     | 1.175    |
| Zhai         | 2006           | China     | Chinese   | Hospital       | 173    | 101    | 28     | 347    | 240          | 52     | 1.313    |
| Brewster     | 2006           | USA       | Caucasian | Population     | 108    | 159    | 38     | 126    | 135          | 49     | 1.585    |
| Zhang        | 2006           | USA       | Caucasian | Population     | 1214   | 1433   | 392    | 1054   | 1173         | 360    | 0.936    |
| Pachkowski   | 2006           | USA       | African   | Population     | 536    | 203    | 22     | 493    | 172          | 11     | 0.834    |
| Pachkowski   | 2006           | USA       | Caucasian | Population     | 504    | 581    | 159    | 480    | 494          | 148    | 1.369    |
| Jin          | 2006           | China     | Chinese   | Population     | 48     | 27     | 8      | 127    | 97           | 27     | 1.658    |
| Bu           | 2006           | USA       | Caucasian | Hospital       | 84     | 84     | 22     | 42     | 43           | 10     | 1.846    |
| IARC-Thai‡   | 2006           | Thailand  | Thai      | Hospital       | 241    | 188    | 31     | 228    | 141          | 19     | 0.23     |
| Seoul‡       | 2006           | Korea     | Korean    | Hospital       | 148    | 119    | 41     | 149    | 144          | 21     | 3.139    |
| ABCFs‡       | 2006           | Australia | Caucasian | Population     | 609    | 669    | 194    | 328    | 391          | 109    | 0.196    |
| GENICA‡      | 2006           | Germany   | Caucasian | Population     | 254    | 290    | 58     | 252    | 299          | 74     | 1.055    |
| LSHTM‡       | 2006           | UK        | Caucasian | Population     | 251    | 251    | 83     | 256    | 274          | 68     | 0.174    |
| Madrid‡      | 2006           | Spain     | Caucasian | Hospital       | 354    | 350    | 104    | 309    | 353          | 108    | 0.201    |
| USRTS‡       | 2006           | USA       | Caucasian | Population     | 314    | 307    | 86     | 425    | 499          | 127    | 1.123    |
| Saadat       | 2007           | Iran      | Iranian   | Population     | 83     | 70     | 33     | 81     | 90           | 16     | 1.683    |
| Silva        | 2007           | Portugal  | Caucasian | Hospital       | 112    | 104    | 25     | 191    | 212          | 53     | 0.251    |
| Costa        | 2007           | Portugal  | Caucasian | Population     | 112    | 109    | 65     | 228    | 338          | 95     | 2.866    |
| Sangrajrang  | 2008           | Thailand  | Thai      | Hospital       | 268    | 201    | 38     | 246    | 158          | 20     | 0.715    |
| Loizidou     | 2008           | Cyprus    | Caucasian | Population     | 506    | 479    | 122    | 520    | 516          | 140    | 0.484    |
| Ali          | 2008           | USA       | Mixed     | Hospital       | 11     | 16     | 13     | 21     | 20           | 7      | 0.382    |
| Smith        | 2008           | USA       | Caucasian | Hospital       | 135    | 141    | 36     | 179    | 181          | 46     | 0.0006   |
| Smith        | 2008           | USA       | African   | Hospital       | 38     | 13     | 1      | 58     | 15           | 1      | 0.0007   |
| Kipikasova   | 2008           | Slovak    | Slovak    | Population     | 15     | 50     | 49     | 17     | 43           | 53     | 2.644    |
| Mitra        | 2008           | India     | Indian    | Population     | 44     | 52     | 54     | 83     | 107          | 35     | 0.003    |
| Syamala      | 2009           | India     | Indian    | Hospital       | 147    | 154    | 58     | 193    | 126          | 48     | 12.743** |
| Hsu          | 2010           | Taiwan    | Chinese   | Hospital       | 198    | 149    | 48     | 276    | 202          | 53     | 3.087    |
| Jelonek      | 2010           | Poland    | Polish    | Population     | 41     | 40     | 13     | 206    | 276          | 69     | 2.535    |
| Sterpone     | 2010           | Italia    | Italian   | Population     | 8      | 24     | 11     | 16     | 10           | 5      | 2.126    |
| Santas       | 2010           | Brazil    | Brazilian | Population     | 24     | 39     | 2      | 24     | 53           | 8      | 7.291**  |
| Zipprich     | 2010           | USA       | Caucasian | Population     | 126    | 115    | 30     | 139    | 141          | 43     | 0.579    |
| Hussien      | 2011           | Egypt     | Egyptian  | Clinics        | 37     | 51     | 12     | 50     | 40           | 10     | 0.227    |
| Lin          | 2011           | China     | Chinese   | Population     | 547    | 367    | 81     | 518    | 402          | 84     | 0.231    |

 Table 1. General Characteristics of Studies Included in the Meta-analysis

 $\uparrow \chi 2$  for testing Hady-Weinberg equilibrium;  $\ddagger$ The seven studies come from the same publication: BCAC, 2006 \*P<0.05; \*\*P<0.01

399Gln allele. In all the three inheritance models of Arg399Gln, there was between-study heterogeneity in the individual studies (all P<0.01 and I<sup>2</sup>>25%), so we analyzed the data using the random-effect model. We found that 399Gln had a weak correlation with the risk of BC (OR =1.15, 95% CI: 1.05–1.27 in the recessive model; and OR =1.15, 95% CI: 1.04–1.27 in the codominant model, Table 2, Figure 1, Figure 2).

We analyzed the relationship of Arg399Gln polymorphisms and BC in different ethnic subgroups: Caucasians, Asians, and Africans. In the recessive model, ten studies dealing with Asians had between-study heterogeneity (P= 0.008 and I<sup>2</sup>=60%), so we analyzed the data using the random-effect model and found that 399Gln (GlnGln vs. ArgGln+ArgArg) increased the risk of BC in Asians (OR=1.54, 95%CI:

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Table 2. Summary OR and 95% CI of XRCC1 Arg399Gln Polymorphism and Breast Cancer Risk

| Contrast                 | N of studies | Ethnicity | OR   | 95%CI     | test for ov | erall effect | test for heterogeneity |         |       |
|--------------------------|--------------|-----------|------|-----------|-------------|--------------|------------------------|---------|-------|
|                          |              | -         |      |           | Z           | Р            | $\chi^2$               | Р       | $I^2$ |
| GlnGln vs. ArgArg        | 44           | Total     | 1.15 | 1.04-1.27 | 2.80**      | 0.005        | 82.05                  | < 0.001 | 48%   |
| (codominant model)       | 10           | Asian     | 1.50 | 1.15-1.97 | 2.95**      | 0.003        | 21.3                   | 0.01    | 58%   |
|                          | 4            | African   | 1.80 | 1.08-3.02 | 2.24*       | 0.03         | 0.13                   | 0.99    | 0%    |
|                          | 30           | Caucasian | 1.05 | 0.95-1.16 | 1.01        | 0.31         | 46.16                  | 0.02    | 37%   |
| GlnGln +ArgGln vs. ArgAr | rg 44        | Total     | 1.04 | 0.98-1.10 | 1.34        | 0.18         | 76.94                  | 0.001   | 44%   |
| (dominant model)         | 10           | Asian     | 1.08 | 0.93-1.25 | 0.98        | 0.33         | 20.83                  | 0.01    | 57%   |
|                          | 4            | African   | 1.30 | 1.07-1.60 | 2.59*       | 0.009        | 3.3                    | 0.35    | 9%    |
|                          | 30           | Caucasian | 1.01 | 0.95-1.07 | 0.29        | 0.77         | 46.14                  | 0.02    | 37%   |
| GlnGln vs. ArgArg +ArgG  | ln 44        | Total     | 1.15 | 1.05-1.27 | 2.93**      | < 0.001      | 87.61                  | < 0.001 | 51%   |
| (recessive model)        | 10           | Asian     | 1.54 | 1.18-2.01 | 3.17**      | 0.002        | 22.42                  | 0.008   | 60%   |
|                          | 4            | African   | 1.59 | 0.96-2.63 | 1.79        | 0.07         | 0.5                    | 0.92    | 0%    |
|                          | 30           | Caucasian | 1.05 | 0.96-1.15 | 1.12        | 0.26         | 47.5                   | 0.02    | 39%   |

\* P<0.05; \*\*P<0.01

|                                   | Breast cancer          |           | Cont        | rol      |                         | Odds Ratio          |       | Odds Ratio                             |
|-----------------------------------|------------------------|-----------|-------------|----------|-------------------------|---------------------|-------|----------------------------------------|
| Study or Subgroup                 | Events                 | Total     | Events      | Total    | Weight                  | M-H, Random, 95% Cl | Year  | M-H, Random, 95% Cl                    |
| 1. Caucasian                      |                        |           |             |          |                         |                     |       |                                        |
| Han 2003                          | 135                    | 986       | 176         | 1337     | 4.0%                    | 1.05 [0.82, 1.33]   | 2003  | t t                                    |
| Moullan 2003                      | 32                     | 254       | 39          | 312      | 2.2%                    | 1.01 [0.61, 1.66]   | 2003  | T                                      |
| Smith 2003a                       | 30                     | 251       | 29          | 267      | 2.0%                    | 1.11 [0.65, 1.92]   | 20038 |                                        |
| Smith 2003b                       | 20                     | 162       | 31          | 300      | 1.7%                    | 1.22 [0.67, 2.22]   | 2003b | T                                      |
| Forsti 2004                       | 20                     | 223       | 31          | 298      | 1.8%                    | 0.85 [0.47, 1.53]   | 2004  |                                        |
| Deligezer 2004                    | 25                     | 151       | 1/          | 133      | 1.5%                    | 1.35 [0.70, 2.63]   | 2004  | <u> </u>                               |
| Figueiredo 2004                   | 55                     | 402       | 5/          | 402      | 2.8%                    | 0.96 [0.64, 1.43]   | 2004  |                                        |
| Mataola 2005                      | 40                     | 470       | 20          | 479      | 0.5%                    | 1 37 [0.35, 2.37]   | 2003  |                                        |
| Datel 2005                        | 40                     | 4/3       | 56          | 529      | 2.4%                    | 1 34 [0.01, 1.99]   | 2005  | +                                      |
| Shen 2005                         | 116                    | 1067      | 130         | 1110     | 3.8%                    | 0 92 [0 70 1 20]    | 2005  | +                                      |
| LSHTM 2006                        | 83                     | 585       | 68          | 598      | 3.2%                    | 1.29 [0.91, 1.82]   | 2006  | -                                      |
| Bu 2006                           | 22                     | 190       | 10          | 95       | 1.2%                    | 1,11 (0.50, 2.46)   | 2006  |                                        |
| Thyagaralan 2006                  | 60                     | 193       | 47          | 322      | 2.6%                    | 2.64 [1.71, 4.08]   | 2006  | -                                      |
| Pachkowski 2006                   | 159                    | 1244      | 148         | 1122     | 4.0%                    | 0.96 [0.76, 1.23]   | 2006  | -                                      |
| GENICA 2006                       | 58                     | 602       | 74          | 625      | 3.0%                    | 0.79 [0.55, 1.14]   | 2006  | -                                      |
| Madrid 2006                       | 104                    | 808       | 108         | 770      | 3.6%                    | 0.91 [0.68, 1.21]   | 2006  | · +                                    |
| ABCFs 2006                        | 194                    | 1472      | 109         | 828      | 3.9%                    | 1.00 [0.78, 1.29]   | 2006  | · +                                    |
| Zhang 2006                        | 392                    | 3039      | 360         | 2587     | 4.8%                    | 0.92 [0.79, 1.07]   | 2006  | . 1                                    |
| USRTS 2006                        | 86                     | 707       | 127         | 1051     | 3.6%                    | 1.01 [0.75, 1.35]   | 2006  | +                                      |
| Brewster 2006                     | 38                     | 305       | 49          | 310      | 2.4%                    | 0.76 [0.48, 1.20]   | 2006  |                                        |
| Costa 2007                        | 65                     | 286       | 95          | 661      | 3.1%                    | 1.75 [1.23, 2.49]   | 2007  | -                                      |
| Silva 2007                        | 25                     | 241       | 53          | 456      | 2.2%                    | 0.88 [0.53, 1.46]   | 2007  |                                        |
| Smith 2008                        | 36                     | 312       | 46          | 406      | 2.4%                    | 1.02 [0.64, 1.62]   | 2008  | I III                                  |
| Kipikasova 2008                   | 49                     | 114       | 53          | 113      | 2.1%                    | 0.85 [0.51, 1.44]   | 2008  |                                        |
| Ali 2008                          | 13                     | 40        |             | 48       | 0.7%                    | 2.82 [1.00, 7.97]   | 2008  | 1                                      |
| Loiziddu 2008                     | 122                    | 1107      | 140         | 11/6     | 3.9%                    | 0.92 [0.71, 1.19]   | 2008  | 1                                      |
| Jeionek 2010<br>Zinnsich 2010     | 13                     | 94        | 69          | 222      | 1.0%                    | 1.12 [0.59, 2.12]   | 2010  | -                                      |
| Elemene 2010                      | 44                     | 49        | 40          | 323      | 0.00/                   | 1 70 10 55 5 901    | 2010  |                                        |
| Subtotal (95% CI)                 |                        | 16166     | 5           | 17486    | 77.2%                   | 1.05 [0.96, 1.15]   | 2010  |                                        |
| Total events                      | 2107                   |           | 2234        |          |                         |                     |       |                                        |
| Heterogeneity: Tau <sup>2</sup> = | 0.02: Chi <sup>2</sup> | = 47.50.  | df = 29 (   | P = 0.02 | ): l <sup>2</sup> = 39% |                     |       |                                        |
| Test for overall effect:          | Z = 1.12 (F            | = 0.26)   |             |          | <i>n</i>                |                     |       |                                        |
|                                   |                        |           |             |          |                         |                     |       |                                        |
| 2. Asian                          |                        |           |             |          |                         |                     |       |                                        |
| Chacko 2005                       | 17                     | 123       | 9           | 123      | 1.0%                    | 2.03 [0.87, 4.75]   | 2005  | · · · ·                                |
| Seoul 2006                        | 41                     | 308       | 21          | 314      | 1.9%                    | 2.14 [1.23, 3.72]   | 2008  |                                        |
| Jin 2006                          | 8                      | 83        | 27          | 251      | 1.1%                    | 0.88 [0.39, 2.03]   | 2006  |                                        |
| Zhai 2006                         | 28                     | 302       | 52          | 639      | 2.3%                    | 1.15 [0.71, 1.87]   | 2006  | - T                                    |
| IARC-Thai 2006                    | 31                     | 460       | 19          | 388      | 1.8%                    | 1.40 [0.78, 2.53]   | 2006  | T                                      |
| Saedat 2007                       | 33                     | 186       | 16          | 187      | 1.6%                    | 2.31 [1.22, 4.35]   | 2007  |                                        |
| Mitra 2008                        | 54                     | 150       | 35          | 225      | 2.2%                    | 3.05 [1.87, 4.99]   | 2008  |                                        |
| Sangrajrang 2008                  | 38                     | 507       | 20          | 424      | 1.9%                    | 1.64 [0.94, 2.86]   | 2008  | <u> </u>                               |
| HSU 2010                          | 48                     | 395       | 53          | 1004     | 2.170                   | 1.25 [0.82, 1.89]   | 2010  | -                                      |
| Subtotal (95% CI)                 | 01                     | 3500      | 04          | 4086     | 10 0%                   | 1 54 [1 18 2 01]    | 2011  | •                                      |
| Total evente                      | 370                    |           | 338         |          | 101070                  | tion future and d   |       |                                        |
| Heterogeneity: Tau <sup>2</sup> = | 0 10 ChP               | = 22 42   | df = 9 (P   | = 0.008  | ): l <sup>2</sup> = 60% |                     |       |                                        |
| Test for overall effect:          | Z = 3 17 (F            | = 0.002   | 1 0 0       | 0.000    | ,                       |                     |       |                                        |
|                                   |                        | 0.000     | <i>''</i>   |          |                         |                     |       |                                        |
| 3. African                        |                        |           |             |          |                         |                     |       |                                        |
| Duell 2001                        | 7                      | 253       | 4           | 266      | 0.5%                    | 1.86 [0.54, 6.45]   | 2001  |                                        |
| Pachkowski 2006                   | 22                     | 761       | 11          | 676      | 1.3%                    | 1.80 [0.87, 3.74]   | 2008  | · +-                                   |
| Smith 2008                        | 1                      | 52        | 1           | 74       | 0.1%                    | 1.43 [0.09, 23.42]  | 2008  |                                        |
| Hussien 2011                      | 12                     | 100       | 10          | 100      | 1.0%                    | 1.23 [0.50, 2.99]   | 2011  |                                        |
| Subtotal (95% CI)                 |                        | 1166      |             | 1116     | 2.9%                    | 1.59 [0.96, 2.63]   |       | -                                      |
| Total events                      | 42                     |           | 26          |          |                         |                     |       |                                        |
| Heterogeneity: Tau* =             | 0.00; Chi*             | = 0.50, c | lf = 3 (P = | = 0.92); | ≓ = 0%                  |                     |       |                                        |
| Test for overall effect:          | Z = 1.79 (F            | e = 0.07) |             |          |                         |                     |       |                                        |
| Total (05% CI)                    |                        | 20244     |             | 22000    | 100.0%                  | 1 46 14 06 4 07     |       |                                        |
| Total guanta                      | 2522                   | P0041     | 2500        | FF000    | 100.076                 | 1.10 [1.00, 1.27]   |       | ľ                                      |
| Hotorogonolty: Tout =             | 2028                   | = 97 64   | 2090        | 0 < 0.00 | 01)-12 = 541            | 92                  |       |                                        |
| Test for overall effect:          | 7 = 2 03 (0            | - 07.01,  | ui - 43 (i  | × 0.00   | or), r = 51             | ~                   |       | 0.01 0.1 1 10 100                      |
| . ous IVI Overan ellect.          | 6.00 (1                | . 0.000   | <b>'</b>    |          |                         |                     |       | involum breast cancer Equation control |

Figure 1. Pooled Gene Effect for Arg399Gln in Relation to Breast Cancer via a Recessive Model among Ethnic Subgroups

1.18–2.01, Table 2, Figure 1). Four articles dealing with Africans had no between-study heterogeneity (P=0.35 and I2=9%) in the dominant model, and in the fixedeffect model meta-analysis, 399Gln (GlnGln+ArgGln vs. ArgArg) was also related with the occurrence of BC (OR =1.30, 95%CI: 1.07-1.60, Table 2, Figure 3).

Thirty studies dealing with Caucasians suggested no associations with BC risk in any of the three inherence models. In the codominant model analysis of stratified subgroups, there were associations both in Asians (OR=1.50, 95%CI: 1.15-1.97) and in Africans 2240 Asian Pacific Journal of Cancer Prevention, Vol 12, 2011

|                                                                 | Breast c                              | ancer                 | Cont        | rol      |                      | Odds Ratio          |       | Odds Ratio                          |
|-----------------------------------------------------------------|---------------------------------------|-----------------------|-------------|----------|----------------------|---------------------|-------|-------------------------------------|
| Study or Subaroup                                               | Events                                | Total                 | Events      | Total    | Weight               | M-H. Random, 95% CI | Year  | M-H. Random, 95% Cl                 |
| 1. Caucasian                                                    |                                       |                       |             |          |                      |                     |       |                                     |
| Moullan 2003                                                    | 145                                   | 254                   | 185         | 312      | 2.0%                 | 0.91 [0.65, 1.28]   | 2003  |                                     |
| Han 2003                                                        | 595                                   | 986                   | 792         | 1337     | 4.0%                 | 1.05 [0.89, 1.24]   | 2003  | +                                   |
| Smith 2003a                                                     | 152                                   | 251                   | 152         | 267      | 1.9%                 | 1.16 [0.82, 1.65]   | 2003a |                                     |
| Smith 2003b                                                     | 92                                    | 162                   | 181         | 300      | 1.6%                 | 0.86 [0.59, 1.27]   | 2003b |                                     |
| Figueiredo 2004                                                 | 234                                   | 402                   | 242         | 402      | 2.5%                 | 0.92 [0.70, 1.22]   | 2004  | -                                   |
| Forsti 2004                                                     | 123                                   | 223                   | 160         | 298      | 1.9%                 | 1.06 [0.75, 1.50]   | 2004  |                                     |
| Deligezer 2004                                                  | 93                                    | 151                   | 83          | 133      | 1.2%                 | 0.97 [0.60, 1.56]   | 2004  |                                     |
| Metsola 2005                                                    | 242                                   | 479                   | 222         | 478      | 2.8%                 | 1.18 [0.91, 1.52]   | 2005  |                                     |
| Patel 2005                                                      | 256                                   | 452                   | 258         | 538      | 2.8%                 | 1.42 [1.10, 1.82]   | 2005  | -                                   |
| Shen 2005                                                       | 655                                   | 1067                  | 666         | 1110     | 3.9%                 | 1.06 [0.89, 1.26]   | 2005  | +                                   |
| Dufloth 2005                                                    | 40                                    | 86                    | 120         | 238      | 1.1%                 | 0.86 [0.52, 1.40]   | 2005  |                                     |
| Madrid 2006                                                     | 454                                   | 808                   | 461         | 770      | 3.5%                 | 0.86 [0.70, 1.05]   | 2006  | -                                   |
| GENICA 2006                                                     | 348                                   | 602                   | 373         | 625      | 3.1%                 | 0.93 [0.74, 1.16]   | 2006  | -                                   |
| Thyagarajan 2006                                                | 136                                   | 193                   | 187         | 322      | 1.7%                 | 1.72 [1.18, 2.52]   | 2006  | <del></del>                         |
| Bu 2006                                                         | 106                                   | 190                   | 53          | 95       | 1.1%                 | 1.00 [0.61, 1.64]   | 2006  |                                     |
| LSHTM 2006                                                      | 334                                   | 585                   | 342         | 598      | 3.1%                 | 1.00 [0.79, 1.25]   | 2006  |                                     |
| Pachkowski 2006                                                 | 740                                   | 1244                  | 642         | 1122     | 4.1%                 | 1.10 [0.93, 1.29]   | 2006  | -                                   |
| USRTS 2006                                                      | 393                                   | 707                   | 626         | 1051     | 3.6%                 | 0.85 [0.70, 1.03]   | 2006  | -                                   |
| Zhang 2006                                                      | 1825                                  | 3039                  | 1533        | 2587     | 5.0%                 | 1.03 [0.93, 1.15]   | 2006  | +                                   |
| ABCFs 2006                                                      | 863                                   | 1472                  | 500         | 828      | 3.9%                 | 0.93 [0.78, 1.11]   | 2006  | +                                   |
| Brewster 2006                                                   | 197                                   | 305                   | 184         | 310      | 2.1%                 | 1.25 [0.90, 1.73]   | 2006  |                                     |
| Silva 2007                                                      | 129                                   | 241                   | 265         | 456      | 2.2%                 | 0.83 [0.61, 1.14]   | 2007  |                                     |
| Costa 2007                                                      | 174                                   | 286                   | 433         | 661      | 2.4%                 | 0.82 [0.61, 1.09]   | 2007  |                                     |
| Ali 2008                                                        | 29                                    | 40                    | 27          | 48       | 0.4%                 | 2.05 [0.84, 5.03]   | 2008  |                                     |
| Smith 2008                                                      | 177                                   | 312                   | 227         | 406      | 2.3%                 | 1.03 [0.77, 1.39]   | 2008  | +                                   |
| Loizidou 2008                                                   | 601                                   | 1107                  | 656         | 1176     | 4.1%                 | 0.94 [0.80, 1.11]   | 2008  | +                                   |
| Kipikasova 2008                                                 | 99                                    | 114                   | 96          | 113      | 0.5%                 | 1.17 [0.55, 2.47]   | 2008  |                                     |
| Jelonek 2010                                                    | 53                                    | 94                    | 345         | 551      | 1.3%                 | 0.77 10.50, 1.201   | 2010  |                                     |
| Steroone 2010                                                   | 35                                    | 43                    | 15          | 31       | 0.3%                 | 4.67 [1.65, 13.23]  | 2010  |                                     |
| Zipprich 2010                                                   | 145                                   | 271                   | 184         | 323      | 2.1%                 | 0.87 10.63, 1.201   | 2010  |                                     |
| Subtotal (95% CI)                                               |                                       | 16166                 |             | 17486    | 72.4%                | 1.01 [0.95, 1.07]   |       | •                                   |
| Total events                                                    | 9465                                  |                       | 10210       |          |                      | -                   |       |                                     |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: 2 | 0.01; Chi²<br>Z = 0.29 (F             | = 46.14,<br>P = 0.77) | df = 29 (i  | 9 = 0.02 | ); I² = 37%          |                     |       |                                     |
| 2. Asian                                                        |                                       |                       |             |          |                      |                     |       |                                     |
| Chacko 2005                                                     | 67                                    | 123                   | 44          | 123      | 1.0%                 | 2 15 [1 29 3 58]    | 2005  |                                     |
| Zhai 2006                                                       | 129                                   | 302                   | 292         | 639      | 2.5%                 | 0.89 [0.67, 1.17]   | 2006  |                                     |
| lin 2006                                                        | 35                                    | 83                    | 124         | 251      | 1 1%                 | 0 75 10 45 1 23     | 2006  |                                     |
| IARC-Thei 2006                                                  | 219                                   | 460                   | 160         | 388      | 2.6%                 | 1 29 10 99 1 701    | 2006  | -                                   |
| Secul 2006                                                      | 160                                   | 308                   | 165         | 314      | 2 2%                 | 0 98 10 71 1 341    | 2006  | -                                   |
| Saadat 2007                                                     | 103                                   | 186                   | 106         | 187      | 1.5%                 | 0.95 (0.63, 1.43)   | 2007  | -                                   |
| Mitra 2008                                                      | 106                                   | 150                   | 142         | 225      | 1.3%                 | 1 41 10 90 2 191    | 2008  |                                     |
| Sangrairang 2008                                                | 239                                   | 507                   | 178         | 424      | 2 7%                 | 1 23 10 95 1 601    | 2008  |                                     |
| Heu 2010                                                        | 197                                   | 395                   | 255         | 531      | 2 7%                 | 1 08 10 83 1 401    | 2010  | +-                                  |
| L in 2011                                                       | 448                                   | 995                   | 486         | 1004     | 3.9%                 | 0.87 10 73 1 041    | 2011  | -                                   |
| Subtotal (95% CI)                                               |                                       | 3509                  |             | 4086     | 21.5%                | 1.08 [0.93, 1.25]   |       | •                                   |
| Total events                                                    | 1703                                  |                       | 1952        |          |                      |                     |       |                                     |
| Heterogeneity: Tau <sup>2</sup> = 1                             | 0.03: Chi <sup>2</sup>                | = 20.83               | df = 9 (P   | = 0.01): | l <sup>2</sup> = 57% |                     |       |                                     |
| Test for overall effect: 2                                      | Z = 0.98 (F                           | P = 0.33)             | u - u (i    | 0.01),   | 1 - 01 /0            |                     |       |                                     |
| 3. African                                                      |                                       |                       |             |          |                      |                     |       |                                     |
| Duell 2001                                                      | 89                                    | 253                   | 68          | 266      | 1.7%                 | 1.58 [1.08, 2.30]   | 2001  |                                     |
| Pachkowski 2006                                                 | 225                                   | 761                   | 183         | 676      | 3.1%                 | 1.13 [0.90, 1.42]   | 2006  | -                                   |
| Smith 2008                                                      | 14                                    | 52                    | 16          | 74       | 0.4%                 | 1.34 [0.58, 3.05]   | 2008  |                                     |
| Hussien 2011                                                    | 63                                    | 100                   | 50          | 100      | 0.9%                 | 1.70 [0.97, 2.99]   | 2011  |                                     |
| Subtotal (95% CI)                                               |                                       | 1166                  |             | 1116     | 6.1%                 | 1.30 [1.07, 1.60]   |       | ◆                                   |
| Total events                                                    | 391                                   |                       | 317         | -        |                      |                     |       |                                     |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: 2 | 0.00; Chi <sup>a</sup><br>Z = 2.59 (F | = 3.30, c<br>= 0.009  | if = 3 (P = | 0.35); I | <sup>2</sup> = 9%    |                     |       |                                     |
| T-1-1 (05% OD                                                   |                                       | 00041                 |             | 00000    | 400.00               | 4 64 10 66 4 100    |       | 1                                   |
| i otal (95% CI)                                                 |                                       | 20841                 | 10.00       | Z2688    | 100.0%               | 1.04 [0.98, 1.10]   |       | 1                                   |
| i otal events                                                   | 11559                                 |                       | 124/9       | 1-00-    | a), 18 - 4 - 4       |                     |       |                                     |
| meterogeneity: 1 au <sup>x</sup> = 1                            | 0.01; Chi#                            | = 76.94,              | ai = 43 (f  | -= 0.00  | 1); [* = 449         | Po l                |       | 0.1 0.2 0.5 1 2 5 10                |
| Lest for overall effect: 2                                      | 2 = 1.34 (F                           | * = 0.18)             |             |          |                      |                     |       | avoure breast cancer Eavoure ocated |

Figure 2. Pooled Gene Effect for Arg399Gln in **Relation to Breast Cancer via a Codominant Model** among Ethnic Subgroups

(OR=1.80, 95%CI: 1.08-3.02, Table 2, Figure 2).

#### Publication bias

The data included in the present study suggested that there might be a publication bias for the comparison of 399Gln versus 399Arg in the dominant and codominant models used. However, when we stratified 399Gln versus 399Arg according to different ethnic groups, there was no publication bias in the subgroups or alternatively the publication bias decreased markedly (Figure 4).

| XRCC1 Arg399Gln and Breast | Cancer Risk | : a Meta- and | alysis of | Case-control | Studies |
|----------------------------|-------------|---------------|-----------|--------------|---------|
|----------------------------|-------------|---------------|-----------|--------------|---------|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Breast c    | ancer     | Cont             | rol                 |                    | Odds Ratio          |       | Odds Ratio          |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------|------------------|---------------------|--------------------|---------------------|-------|---------------------|--|--|
| Study or Subgroup                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Events      | Total     | Events           | Total               | Weight             | M-H, Random, 95% Cl | Year  | M-H, Random, 95% Cl |  |  |
| 1. Caucasian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |           |                  |                     |                    |                     |       |                     |  |  |
| Han 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 135         | 526       | 176              | 721                 | 4.1%               | 1.07 [0.83, 1.39]   | 2003  | · +                 |  |  |
| Moullan 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 32          | 141       | 39               | 166                 | 2.2%               | 0.96 [0.56, 1.63]   | 2003  | +                   |  |  |
| Smith 2003a                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 30          | 129       | 29               | 144                 | 1.9%               | 1.20 [0.67, 2.14]   | 2003a |                     |  |  |
| Smith 2003b                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 20          | 90        | 31               | 150                 | 1.7%               | 1.10 10.58, 2.071   | 2003b | +                   |  |  |
| Figueiredo 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 55          | 223       | 57               | 217                 | 2.8%               | 0.92 [0.60, 1.41]   | 2004  | +                   |  |  |
| Deligezer 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 25          | 83        | 17               | 67                  | 1.4%               | 1 27 10 62 2 611    | 2004  |                     |  |  |
| Foreti 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 20          | 120       | 31               | 160                 | 1.8%               | 0 89 10 48 1 651    | 2004  | -                   |  |  |
| Motoolo 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 40          | 202       | 97               | 202                 | 2.6%               | 1 24 10 94 2 141    | 2005  |                     |  |  |
| Ohan 000E                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 40          | 203       | 400              | 203                 | 2.076              | 1.04 [0.04, 2.14]   | 2003  | <b>_</b>            |  |  |
| Direct 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 7           | 520       | 130              | 400                 | 4.00/              | 0.00 [0.72, 1.20]   | 2000  |                     |  |  |
| Dulloin 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             | 00        | 20               | 130                 | 1.076              | 0.90 [0.30, 2.27]   | 2005  |                     |  |  |
| Patel 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 61          | 257       | 00               | 330                 | 2.9%               | 1.56 [1.04, 2.34]   | 2005  |                     |  |  |
| Bu 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 22          | 106       | 10               | 52                  | 1.1%               | 1.10 [0.48, 2.53]   | 2006  |                     |  |  |
| Thyagarajan 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 60          | 117       | 47               | 182                 | 2.4%               | 3.02 [1.85, 4.94]   | 2006  |                     |  |  |
| ABCFs 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 194         | 803       | 109              | 437                 | 4.0%               | 0.96 [0.73, 1.26]   | 2006  | I                   |  |  |
| USRTS 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 86          | 400       | 127              | 552                 | 3.7%               | 0.92 [0.67, 1.25]   | 2006  | T                   |  |  |
| Brewster 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 38          | 146       | 49               | 175                 | 2.4%               | 0.90 [0.55, 1.49]   | 2006  | T                   |  |  |
| Zhang 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 392         | 1606      | 360              | 1414                | 5.0%               | 0.95 [0.80, 1.12]   | 2006  | Ť                   |  |  |
| GENICA 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 58          | 312       | 74               | 326                 | 3.1%               | 0.78 [0.53, 1.14]   | 2006  | -                   |  |  |
| LSHTM 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 83          | 334       | 68               | 324                 | 3.2%               | 1.24 [0.86, 1.79]   | 2006  |                     |  |  |
| Pachkowski 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 159         | 663       | 148              | 628                 | 4.2%               | 1.02 [0.79, 1.32]   | 2006  | +                   |  |  |
| Madrid 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 104         | 458       | 108              | 417                 | 3.7%               | 0.84 [0.62, 1.15]   | 2006  | -                   |  |  |
| Silva 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 25          | 137       | 53               | 244                 | 2.2%               | 0.80 [0.47, 1.37]   | 2007  | -                   |  |  |
| Costa 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 65          | 177       | 95               | 323                 | 3.1%               | 1.39 (0.94, 2.05)   | 2007  | · +-                |  |  |
| Smith 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 36          | 171       | 48               | 225                 | 2 4%               | 1 04 10 64 1 691    | 2008  | +                   |  |  |
| Loizidou 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 122         | 628       | 140              | BBO                 | 4.0%               | 0.00 0.68 1 181     | 2008  | +                   |  |  |
| Kinikasova 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 40          | 64        | 53               | 70                  | 1 296              | 1 05 10 47 2 321    | 2000  |                     |  |  |
| All 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 10          | 24        | 7                | 20                  | 0.49/              | 3 55 14 40 44 461   | 2000  |                     |  |  |
| All 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 10          | 480       |                  | 400                 | 0.0%               | 0.00 [1.10, 11.40]  | 2000  | -                   |  |  |
| Zipprich 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 30          | 100       | 43               | 102                 | 2.276              | 0.77 [0.46, 1.30]   | 2010  |                     |  |  |
| Jeionek 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 13          | 54        | 69               | 2/5                 | 1.5%               | 0.95 [0.48, 1.87]   | 2010  |                     |  |  |
| Sterpone 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 11          | 19        | 5                | 21                  | 0.5%               | 4.40 [1.13, 17.07]  | 2010  |                     |  |  |
| SUDIOIAI (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |             | 8808      |                  | 9510                | 10.8%              | 1.05 [0.95, 1.16]   |       | 1                   |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 2107        |           | 2234             |                     |                    |                     |       |                     |  |  |
| Heterogeneity: Tau <sup>2</sup> =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.02; ChP   | = 46.16,  | df = 29 (F       | <sup>o</sup> = 0.02 | ); P = 37%         |                     |       |                     |  |  |
| Test for overall effect:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Z = 1.01 (F | P = 0.31) |                  |                     |                    |                     |       |                     |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |             |           |                  |                     |                    |                     |       |                     |  |  |
| 2. African                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |           |                  |                     |                    |                     |       |                     |  |  |
| Duell 2001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 7           | 171       | 4                | 202                 | 0.6%               | 2.11 [0.61, 7.34]   | 2001  | +                   |  |  |
| Pachkowski 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 22          | 558       | 11               | 504                 | 1.4%               | 1.84 [0.88, 3.83]   | 2006  |                     |  |  |
| Smith 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1           | 39        | 1                | 59                  | 0.1%               | 1.53 [0.09, 25.15]  | 2008  |                     |  |  |
| Hussien 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 12          | 49        | 10               | 60                  | 0.9%               | 1.62 (0.63, 4.15)   | 2011  |                     |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |             | 817       |                  | 825                 | 3.0%               | 1.80 [1.08, 3.02]   |       | •                   |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 42          |           | 26               |                     |                    |                     |       |                     |  |  |
| Heterogeneity: Tau <sup>a</sup> =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.00: Chi*  | = 0.13. d | f = 3 (P =       | 0.99)-1             | <sup>2</sup> = 0%  |                     |       |                     |  |  |
| Test for overall effect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 7 = 2 24 /  | 2 = 0.03) |                  | 0.00), 1            |                    |                     |       |                     |  |  |
| reation overall enoce.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | c - c.c+ (r | - 0.00)   |                  |                     |                    |                     |       |                     |  |  |
| 3. Asian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |             |           |                  |                     |                    |                     |       |                     |  |  |
| Chasks 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 47          | 70        | ~                | 00                  | 1.09               | 2 66 14 44 6 441    | 200*  |                     |  |  |
| Chacko 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1/          | 13        | 9                | 00                  | 1.0%               | 2.00 [1.11, 0.41]   | 2005  |                     |  |  |
| IARC-Thai 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 31          | 212       | 19               | 24/                 | 1.976              | 1.04 [0.00, 2.01]   | 2000  | -                   |  |  |
| Seoul 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 41          | 189       | 21               | 1/0                 | 2.0%               | 1.97 [1.11, 3.49]   | 2006  |                     |  |  |
| Zhai 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 28          | 201       | 52               | 399                 | 2.4%               | 1.08 [0.66, 1.77]   | 2006  |                     |  |  |
| Jin 2006                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 8           | 56        | 27               | 154                 | 1.1%               | 0.78 [0.33, 1.85]   | 2006  |                     |  |  |
| Saadat 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 33          | 116       | 16               | 97                  | 1.6%               | 2.01 [1.03, 3.94]   | 2007  |                     |  |  |
| Sangrajrang 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 38          | 306       | 20               | 266                 | 2.0%               | 1.74 [0.99, 3.08]   | 2008  |                     |  |  |
| Mitra 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 54          | 98        | 35               | 118                 | 2.0%               | 2.91 [1.66, 5.10]   | 2008  |                     |  |  |
| Hsu 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 48          | 246       | 53               | 329                 | 2.8%               | 1.26 [0.82, 1.94]   | 2010  |                     |  |  |
| Lin 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 81          | 628       | 84               | 602                 | 3.5%               | 0.91 [0.66, 1.27]   | 2011  | <b>†.</b>           |  |  |
| Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |             | 2185      |                  | 2470                | 20.2%              | 1.50 [1.15, 1.97]   |       | •                   |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 379         |           | 336              |                     |                    |                     |       |                     |  |  |
| Heterogeneity: Tau <sup>2</sup> =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.10; Chi#  | = 21.30.  | df = 9 (P        | = 0.01):            | <sup>2</sup> = 58% |                     |       |                     |  |  |
| Test for overall effect :                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Z = 2.95 (F | = 0.003   | )                |                     |                    |                     |       |                     |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |             |           | -                |                     |                    |                     |       |                     |  |  |
| Total (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |             | 11810     |                  | 12805               | 100.0%             | 1.15 [1.04, 1.27]   |       | •                   |  |  |
| Total events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 2528        |           | 2596             |                     |                    |                     |       |                     |  |  |
| Heterogeneity: Tout =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | n na: Ch#   | = 82.05   | df = 43 /4       | 2 = 0 00            | 03)· I# = 44       | 8%                  |       |                     |  |  |
| Toet for overall effect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 7 = 2 80 /  | 02.00,    | u. – – u (r<br>) | - 0.00              |                    |                     |       | 0.01 0.1 1 10 100   |  |  |
| rest for overall effect a control of a contr |             |           |                  |                     |                    |                     |       |                     |  |  |

Figure 3. Pooled Gene Effect for Arg399Gln in Relation to Breast Cancer via a Dominant Model among Ethnic Subgroups

## Discussion

BC is a multifactorial disease that results from the complex interactions between genetic and environmental factors. From our meta-analysis of the combined 44 studies, XRCC1 Arg399Gln was associated with a trend of increased BC risk. Based on our results, individuals who had the Gln allele were more likely to have BC (recessive model: OR =1.15, 95% CI: 1.05–1.27; codominant model: OR =1.15, 95% CI: 1.04–1.27). This is biologically plausible because 399Gln is located at the carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase interacting domain and has been shown to reduce DNA repair capacity (Duell et al., 2000), and somatic glycophorin A mutations were significantly higher in 399Gln homozygotes than in heterozygotes (Lunn et al., 1999). Furthermore, in the recessive model analysis of stratified subgroups, Arg399Gln had a higher risk correlation with BC in Asians (OR =1.54, 95% CI: 1.18–2.01) and Africans (OR =1.59, 95% CI: 0.96–2.63) than in Caucasians (OR =1.05, 95% CI: 0.96–1.15). Considering the lower frequency of Gln/Gln, the population-attributable risk was limited among Asians.

There is an obvious publication bias of studies for the comparison of 399Gln versus 399Arg, but when we stratified the studies into different ethnic subgroups, the publication bias disappeared or decreased. Moreover, though there was moderate heterogeneity between the combined studies of XRCC1 Codon399, when we analyzed the Arg399Gln polymorphism in different ethnic subgroups, the between-study heterogeneity decreased markedly. These results suggest that the publication bias and heterogeneity may be partly due to the variable effects of stratified ethnic subgroups, and some genetic polymorphisms may be associated with risk of some diseases in a specific ethnic subgroup.

XRCC1 is very important for efficient base excision and single-strand break repair. The interactions of XRCC1 and its substrate result in assembly of the repair complex at the site of damage and regulate the activity of several repair enzymes, particularly poly (ADP-ribose) polymerase 1 (PARP1), ligase III and polynucleotide kinase 3'-phosphatase (Caldecott et al., 1996). Cells of rodents lacking XRCC1 are very sensitive to genetoxins and show increased genetic instability (Caldecott et al., 1994; 1996). XRCC1 has two BRCA1 carboxyl-terminal (BRCT) domains (BRCT1 and BRCT2), located centrally and at the C-terminal end, respectively. The centre of BRCT1 domain binds to and down-regulates the single-strand breaks and gaps recognition protein PARP1 and is required for efficient SSBR during both G1 and S/G2 phases of the cell cycle. The mechanism by which XRCC1 399Gln may contribute to BC is, however, unknown. Since XRCC1 is a recruiting protein for BER, the possibility exists that 399Gln acts by modifying the interactions with other BER proteins. In particular, APE1 and PARP1 are candidates, because they interact with XRCC1 through the BRCT1 domain that contains codon 399 (Masson



Figure 4. Funnel Plot of Comparison for Publication Bias in Arg399Gln Ethnicity Subgroup Analysis via (a) Recessive Model, (b) Codominant Model, and (c) Dominant Model

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et al., 1998; Marsin et al., 2003). The polymorphism Arg399Gln is located close to BRCT1's C-terminal boundary. The mutation in this domain will change XRCC1's structure and maybe disrupt the combination of BRCT1 and PARP1. Finally, the involvement of DNA repair defects in the development of BC is relevant. This is because mutations in the two wellknown BC genes (BRCA1 and BRCA2) contribute to DNA repair deficiency (Novak et al., 2009), as well as their interacting proteins. Furthermore, XRCC1 probably interacts with the breast cancer gene proteins because it has two BRCA1 carboxyl-terminal (BRCT) domains.

In conclusion, our meta-analyses, under both recessive and dominant models, indicate that the Arg399Gln polymorphism associates with an increased risk of breast cancer, especially in the Asian population. With the large population size for our analyses, we feel that the results are reliable. However, more comparative studies are needed to evaluate associations in other ethnic groups. Furthermore, mechanistic studies need to be conducted to evaluate the underlying reasons for the association.

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