Assessing Interactions between Common Genetic Variant on 2q35 and Hormone Receptor Status with Breast Cancer Risk: Evidence Based on 26 Studies

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Abstract

Genome-wide association studies have identified 2q35-rs13387042 as a new breast cancer (BC) susceptibility locus in populations of European descent. Since then, the relationship between 2q35-rs13387042 and breast cancer has been reported in various ethnic groups; however, these studies have yielded inconsistent results. To investigate this inconsistency, we performed a meta-analysis of 26 studies involving a total of 101,529 cases and 167,363 controls for 2q35-rs13387042 polymorphism to evaluate its effect on genetic susceptibility for breast cancer. An overall random effects odds ratio of 1.14 (95% CI: 1.11–1.16, P = 10−5) was found for rs13387042-A variant. Significant results were also observed using dominant (OR = 1.14, 95% CI: 1.12–1.17, P < 10−5), recessive (OR = 1.17, 95% CI: 1.13–1.21, P < 10−5) and co-dominant genetic model (heterozygous: OR = 1.15, 95% CI: 1.12–1.19, P < 10−5; homozygous: OR = 1.20, 95% CI: 1.15–1.24, P < 10−5). There was strong evidence of heterogeneity, which largely disappeared after stratification by ethnicity. Significant associations were found in East Asians, and White populations when stratified by ethnicity; while no significant associations were observed in Africans and other ethnic populations. An association was observed for both ER-positive (OR = 1.17, 95% CI: 1.15–1.19; P = 10−5) and ER-negative disease (OR = 1.08, 95% CI: 1.04–1.13; P < 10−5) and both progesterone receptor (PR)-positive (OR = 1.18, 95% CI: 1.15–1.21; P < 10−5) and PR-negative disease (OR = 1.10, 95% CI: 1.05–1.15; P < 10−5). In conclusion, this meta-analysis demonstrated that the A allele of 2q35-rs13387042 is a risk factor associated with increased breast cancer susceptibility.

Introduction

Breast cancer is the most common cancer and the leading cause of cancer death among women worldwide, accounting for 23% of the total cancer cases and 14% of the cancer deaths in 2008 [1]. The mechanism of breast carcinogenesis is still not fully understood. It has been suggested that environmental and genetic factors may affect the individual’s susceptibility to cancer [2]. High-penetrance breast cancer susceptibility genes, such as BRCA1 and BRCA2, explain only a small fraction of breast cancers in the general population because of their low mutation rates [3]. Over the past decades, the candidate approach has ever been successfully employed to identify BC susceptibility, such as ATM and XRCG1 of DNA repair genes have been confirmed to be associated with BC risk [4–6]. However, most of the genetic variants identified by candidate-gene studies have not been replicated [7]. Recently, several genome-wide association studies (GWAS) have been conducted and identified genetic susceptibility loci that are associated with breast cancer risk [8–11]. The rs13387042 polymorphism at chromosome 2q35 has been identified as a new hotspot for breast cancer susceptibility by a recent GWA study [12]. Associations between the 2q35-rs13387042 polymorphism and breast cancer have been independently replicated by subsequent studies; however, a proportion of them have produced contrary results. Growing evidence suggests substantial heterogeneity by tumor subtype, defined by hormone receptor status, for association with the polymorphism [9,12]. Because estrogen receptor (ER) and progesterone receptor (PR) statuses are the major markers of breast cancer subtypes, these observations suggest that inherited risk variants of these subtypes may vary. The lack of concordance across many of these studies reflects limitation in the studies, such as small sample size, ethnic difference, and study design. With the increased studies in recent years among East Asians, Africans and some other ethnic populations, there is a need to reconcile this inconsistency and to clarify the problems in previous studies. We therefore performed a meta-analysis of the published studies to clarify this inconsistency and to establish a comprehensive picture of the relationship between 2q35 rs13387042 polymorphism and breast cancer.
Materials and Methods

Literature search strategy and inclusion criteria

Papers published before the end of January 2013 were identified through a search of PubMed, SCOPUS, ISI web of knowledge, Embase and Cochrane databases. Search term combinations were keywords relating to the chromosome 2q35 (e.g., “chromosome 2q35”, and “rs13387042”) in combination with words related to breast cancer (e.g., “breast cancer”, “breast carcinoma”, “malignant breast neoplasm”) and polymorphism or variation. The titles and abstracts of potential articles were screened to determine their relevance, and any clearly irrelevant studies were excluded. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. In addition, all reference lists from the main reports and relevant reviews were hand searched for additional eligible studies not indexed by Medline.

Inclusion criteria and data extraction

Eligible studies had to meet all of the following criteria: (1) original papers containing independent data which have been published in peer-reviewed journal, (2) case–control or cohort studies, (3) genotype distribution information or odds ratio (OR) with its 95% confidence interval (CI) and P-value, (4) genotype distribution of control group must be consistent with Hardy–Weinberg equilibrium (HWE).

For each qualified study, the following information was extracted independently and entered into separate databases by two authors: first author’s surname, publication date, ethnicity, source of control subjects, genotyping method, age, tumor stage, histopathological subtype, ER status, PR status, total number of cases and controls, and genotype frequency in cases and controls. The results were compared, and disagreements were discussed among all authors and resolved with consensus. For studies including subjects of different ethnic groups, data were extracted separately according to ethnicity. If multiple published reports from the same study population were available, we included only the one with largest sample size and the most detailed information. Meanwhile, different case–control groups in one study were considered as independent studies.

Statistical methods

The meta-analysis examined the association between the rs13387042 polymorphism and the risk of BC, for the: (i) allele contrast, (ii) dominant, (iii) recessive, and (iv) co-dominant models [13]. Crude ORs with 95% CIs were calculated using raw data, according to the method of Woolf [14]. Cochran’s Q-statistic test was performed to assess possible heterogeneity in the combined studies [15]. Both fixed-effects (Mantel–Haenszel method) [16] and random-effects (DerSimonian–Laird method) [17] models were performed to calculate the pooled ORs. Owing to a priori assumptions about the likelihood of heterogeneity between primary studies, the random-effects model, which usually is more conservative, was chosen. Sub-group analyses and meta-regression were used to explore heterogeneity [18]. Ethnicity, study design (GWAS vs. candidate gene study), ER status (ER-positive vs. ER-negative), PR status (PR-positive vs. PR-negative) and invasiveness (invasive vs. in situ) were prespecified as characteristics for assessment of heterogeneity. Ethnic group was defined as White (i.e., people of European origin), East Asian (e.g., Chinese, Japanese, and Korean), African and others (e.g., Jew and Hawaiian). One-way sensitivity analysis was performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. Funnel plots and the Egger’s test were used to examine the influence of publication bias (linear regression analysis) [19]. All P values are two-sided at the P = 0.05 level. All of the statistical tests used in this meta-analysis were performed by STATA version 10.0 (Stata Corporation, College Station, TX).

Results

Characteristics of included studies

The combined search yielded 113 references. 87 articles were excluded because they clearly did not meet the criteria or overlapping references (Figure S1). Finally, a total of 26 eligible association studies were included involving 101,529 breast cancer cases and 167,363 controls [12,20–44]. Of the cases, 80% were White, 12% were East Asian, 7% were African descent, and 1% were of other ethnic origins. The main study characteristics were summarized in Table 1.

Association of 2q35-rs13387042 with breast cancer

There was a wide variation in the A allele frequency of the rs13387042 polymorphism among the controls across different ethnicities, ranging from 0.05 to 0.75 (Table 1). For East Asian controls, the A allele frequency was 0.12 (95% CI: 0.08–0.16), which was lower than that in White controls (0.51; 95% CI: 0.48–0.53) and African controls (0.72; 95% CI: 0.65–0.79).

The main results of this meta-analysis were listed in Table 2 and Table S1. In the overall analysis, the rs13387042 polymorphism was significantly associated with elevated breast cancer risk with a per-allele OR of 1.14 [95% CI: 1.11–1.16, P(Z) < 0.01; Figure 1], with corresponding results under dominant and recessive genetic models of 1.14 [95% CI: 1.12–1.17, 1.15–1.19, P(Z) < 0.01] and 1.17 [95% CI: 1.13–1.21, 1.15–1.24, P(Z) < 0.01]. Significant associations were also found for co-dominant genetic model [heterozygous: OR = 1.15, 95% CI: 1.12–1.19, 1.14–1.20, P(Z) < 0.01; homozygous: OR = 1.20, 95% CI: 1.15–1.24, 1.13–1.25, P(Z) < 0.01]. In the stratified analysis by ethnicity, significantly increased risks were found among East Asians [A allele: OR = 1.12, 95% CI: 1.03–1.21, P(Z) = 0.004, P(Q) = 0.18; dominant model: OR = 1.10, 95% CI: 1.03–1.18, P(Z) = 0.003, P(Q) = 0.27; recessive model: OR = 1.09, 95% CI: 1.02–1.19, P(Z) = 0.01, P(Q) = 0.63; heterozygous: OR = 1.11, 95% CI: 1.04–1.20, P(Z) = 0.001, P(Q) = 0.33; homozygous: OR = 1.10, 95% CI: 1.02–1.19, P(Z) < 0.01, P(Q) = 0.25]. White populations [A allele: OR = 1.14, 95% CI: 1.12–1.17, P(Z) < 0.01, P(Q) = 0.02; dominant model: OR = 1.16, 95% CI: 1.13–1.18, P(Z) < 0.01, P(Q) = 0.59; recessive model: OR = 1.20, 95% CI: 1.14–1.24, P(Z) < 0.01, P(Q) < 0.01; heterozygous: OR = 1.15, 95% CI: 1.13–1.18, P(Z) < 0.01, P(Q) = 0.002; homozygous: OR = 1.21, 95% CI: 1.15–1.25, P(Z) < 0.01, P(Q) < 0.01]. However, no significant associations were detected among African [A allele: OR = 1.07, 95% CI: 0.99–1.16, P(Z) = 0.17, P(Q) = 0.03] and other ethnic populations [A allele: OR = 1.24, 95% CI: 0.59–2.61, P(Z) = 0.57, P(Q) < 0.01]. Subsidiary analyses of study design yielded a per-allele OR for GWAS of 1.16 [95% CI: 1.14–1.19, P(Q) < 0.01] and for candidate gene study of 1.11 [95% CI: 1.08–1.15, P(Q) < 0.01].

We further performed analyses to test for differences in the associations of the polymorphism with breast cancer risk with respect to different prognostic factors. Specifically, we compared estrogen receptor–positive (ER+) case subjects with ER-negative (ER−) case subjects, and in a similar fashion progesterone receptor-positive (PR+) case subjects with receptor-negative (PR−) case subjects. Stratification of tumors by ER status...
Table 1. Characteristics of the studies included in the meta-analysis.

| Study                      | Year | Ethnicity                  | Genotyping method    | No. of cases/controls | Control source | RAF in cases/controls | Study design |
|----------------------------|------|----------------------------|----------------------|-----------------------|-----------------|-----------------------|--------------|
| Stacey [12]                | 2008 | European                   | SNP Array            | 4420/17365            | GP              | 0.54/0.50             | GWAS         |
| Milne [20]                 | 2009 | European, Asian            | SNP Array, iPLEX     | 31511/35969           | GP, HP          | 0.55/0.51             | GWAS         |
| Zheng [21]                 | 2009 | African                    | Massarray            | 810/1784              | GP              | 0.77/0.74             | Candidate gene |
| Antoniou [22]              | 2009 | European, American         | TaqMan, iPLEX        | 7805/6675             | GP              | 0.53/0.51             | Candidate gene |
| Reeves [23]                | 2010 | British                    | TaqMan               | 10306/10393           | GP              | 0.54/0.50             | Candidate gene |
| Hemminki [24]              | 2010 | European                   | iPLEX                | 1415/1830             | GP              | 0.57/0.54             | Candidate gene |
| Zheng [25]                 | 2010 | Chinese                    | SNP Array            | 3039/3082             | GP              | 0.11/0.11             | Candidate gene |
| Barnholtz-Sloan [26]       | 2010 | American                   | GoldenGate           | 1230/1117             | GP              | 0.55/0.53             | Candidate gene |
| Teraoka [27]               | 2011 | European, American         | GoldenGate           | 704/1386              | GP              | 0.55/0.52             | Candidate gene |
| Fletcher [28]              | 2011 | British                    | SNP Array, GoldenGate| 7643/7443             | GP              | 0.53/0.52             | GWAS         |
| Campa [29]                 | 2011 | American, European, African, Asian, Hawaiian | SNP Array, TaqMan | 8314/11589 | GP | 0.52/0.49 | GWAS |
| Jiang [30]                 | 2011 | Chinese                    | SNaPshot             | 492/510               | GP              | 0.12/0.10             | Candidate gene |
| Li [31]                    | 2011 | European                   | SNP Array            | 1557/4584             | GP              | 0.48/0.47             | Candidate gene |
| Chen [32]                  | 2011 | African                    | SNP Array            | 3016/2745             | GP              | 0.73/0.72             | Candidate gene |
| Slattery [33]              | 2011 | American                   | TaqMan               | 1733/2041             | GP              | 0.53/0.52             | Candidate gene |
| Stevens [34]               | 2011 | European, American, Australian | iPLEX               | 2977/4976             | GP              | 0.53/0.51             | Candidate gene |
| Hutter [35]                | 2011 | African                    | SNP Array            | 316/7486              | GP              | 0.69/0.70             | Candidate gene |
| Dai [36]                   | 2012 | Chinese                    | TaqMan               | 1771/1851             | GP              | 0.13/0.11             | Candidate gene |
| He [37]                    | 2012 | European                   | TaqMan               | 3683/34174            | GP              | 0.55/0.50             | Candidate gene |
| Shan [38]                  | 2012 | Tunisian                   | TaqMan               | 640/367               | GP              | 0.58/0.55             | Candidate gene |
| Kim [39]                   | 2012 | Korean                     | SNP Array, TaqMan    | 2257/2052             | GP              | 0.10/0.10             | GWAS         |
| Huo [40]                   | 2012 | African                    | GoldenGate           | 1509/1383             | GP              | 0.77/0.75             | Candidate gene |
| Lin [41]                   | 2012 | Chinese                    | SNP Array            | 88/69                 | GP              | 0.15/0.06             | Candidate gene |
| Harlid [42]                | 2012 | European                   | MassARRAY            | 3393/4837            | GP              | 0.53/0.50             | Candidate gene |
| Sueta [43]                 | 2012 | Japanese                   | TaqMan               | 697/1394              | HP              | 0.10/0.10             | Candidate gene |
| Rinella [44]               | 2013 | Jewish                     | KASPar               | 203/263              | GP              | 0.66/0.52             | Candidate gene |

GP: general population, HP: hospital patient, RAF: risk allele frequency.
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indicated that rs13387042 had a stronger association with ER-positive [per-allele OR = 1.17, 95% CI: 1.15–1.19; P(Z) = 0.47] than ER-negative tumors [per-allele OR = 1.08, 95% CI: 1.04–1.13; P(Z) = 0.18] (Figure 2). Similarly, a stronger association was also observed for the polymorphism with PR-positive tumors [per-allele OR = 1.18, 95% CI: 1.15–1.21; P(Z) = 0.57] compared with PR-negative tumors [per-allele OR = 1.10, 95% CI: 1.05–1.15; P(Z) = 0.16] (Figure 3).

The effect of the polymorphism was assessed for over-all breast cancer risk. No association was established between the polymorphism and tumor invasiveness. The data on tumor invasiveness were available in three studies, which included 20442 breast cancer patients. For 2q35-rs13387042, there appeared to be a similar per-allele OR for in situ cancer [per-allele OR = 1.17, 95% CI: 1.04–1.13; P(Z) = 0.27] as compared to invasive cancer [per-allele OR = 1.19, 95% CI: 1.15–1.22; P(Z) = 0.51].

Significant heterogeneity was present among the 44 data sets from 26 studies of the rs13387042 polymorphism (P<0.05). In meta-regression analysis, sample size (P = 0.21), source of controls (P = 0.13) and genotyping method (P = 0.73) did not significantly explain such heterogeneity. By contrast, ethnicity (P = 0.004) was significantly correlated with the magnitude of the genetic effect.

Sensitivity analyses and publication bias

Influence analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no individual study significantly affected the pooled OR, thus suggesting that the results of this meta-analysis are stable (data not shown). The shape of the funnel plot did not indicate any evidence of obvious asymmetry (Figure S2), thus suggesting no publication bias among the studies included. The statistical results still did not show preferential publication of positive findings in smaller studies (Begg’s test, P = 0.27; Egger’s test, P = 0.63).

Discussion

GWAS have led to the identification of multiple new genetic variants associated with breast cancer risk. Most of these breast cancer GWAS and replication studies have been conducted in European populations [11,12,24,28] and to a lesser extent in East Asians [25,30,36]. However, there are significant differences in allele frequencies and the prevalence of breast cancer among different populations. It is, therefore, important to quantitatively assess the effects of the GWAS-identified markers in different ethnic populations and explore potential heterogeneity of published data. To the best of our knowledge, this is the first...
Table 2. Meta-analysis of the 2q35-rs13387042 polymorphism on breast cancer risk.

| Sub-group analysis | No. of data sets | No. of cases/controls | A allele Dominant model | P (Z) | P (Q) | a P (Q) | OR (95%CI) | P (Z) | P (Q) | a P (Q) | OR (95%CI) | P (Z) | P (Q) |
|--------------------|------------------|-----------------------|------------------------|-------|-------|--------|------------|-------|-------|--------|------------|-------|-------|
| Total              | 44               | 101,529/167,363       | 1.14 (1.11–1.16)       | 0.11  | 0.22  | 0.38   | 1.17 (1.13–1.21) | 0.2   | 0.59  | 0.77   | 1.20 (1.14–1.27) | 0.25  | 1.18 |
| Ethnicity          |                  |                       |                        |       |       |        |            |       |       |        |            |       |       |
| White              | 26               | 82,147/140,849        | 1.16 (1.13–1.18)       | 0.59  | 0.27  | 0.90   | 1.09 (1.01–1.17) | 0.01  | 0.63  | 0.22   | 1.06 (0.94–1.21) | 0.37  | 0.52 |
| East Asian         | 9                | 116,817/117,773       | 1.16 (1.12–1.17)       | 0.05  | 0.77  | 0.57   | 1.16 (1.10–1.21) | 0.09  | 0.27  | 0.17   | 1.09 (1.02–1.19) | 0.37  | 0.52 |
| African            | 7                | 669,241/94,193        | 1.04 (1.00–1.09)       | 0.13  | 0.47  | 0.07   | 1.04 (1.00–1.10) | 0.14  | 0.62  | 0.11   | 1.05 (1.02–1.09) | 0.04  | 0.07 |
| Other              | 2                | 340,548               | 1.20 (1.19–1.21)       | 0.20  | 0.06  | 0.01   | 1.16 (1.13–1.21) | 0.35  | 0.03  | 0.01   | 1.15 (1.13–1.19) | 0.20  | 1.13 |
| Study design       | 5                | 59,457/44,181         | 1.16 (1.14–1.19)       | 0.20  | 0.06  | 0.01   | 1.16 (1.14–1.19) | 0.35  | 0.03  | 0.01   | 1.15 (1.13–1.19) | 0.20  | 1.13 |
| GWAS               | 5                | 47,934/42,945         | 1.16 (1.14–1.19)       | 0.20  | 0.06  | 0.01   | 1.16 (1.14–1.19) | 0.35  | 0.03  | 0.01   | 1.15 (1.13–1.19) | 0.20  | 1.13 |
| Candidate gene     | 39               | 0.001                 |                         |       |       |        |            |       |       |        |            |       |       |
| *Cochran's chi-square Q statistic test used to assess the heterogeneity between subgroups.*
| **Cochran's chi-square Q statistic test used to assess the heterogeneity in subgroups.**

A number of factors predict breast cancer, however, detailed pathogenesis mechanisms of breast cancer remain a matter of speculation. 2q35-rs13387042 is located in a 90-kb region of high linkage disequilibrium that contains neither known genes nor non coding RNAs [12, 29]. The causal variant (or variants) in this region has (have) not been determined, and it is possible that one or more SNPs may confer a higher risk than 2q35-rs13387042. Thus, functional studies in this region are likely to lead to a better understanding of mechanisms of carcinogenesis and progression of breast cancer. However, the ORs we obtained were small with narrow CIs. This indicates that when considered alone as a genetic
| Study ID       | Odds Ratio (95% CI) | Weight |
|---------------|---------------------|---------|
| North American | 1.21 (0.99, 1.47)   | 1.06    |
| East Asian    |                     |         |
| Campa (MEC) (2011) | 1.34 (1.16, 1.56)   | 1.60    |
| Campa (EPIC) (2011) | 1.10 (0.82, 1.19)   | 3.73    |
| Campa (MEC) (2011) | 1.24 (1.12, 1.38)   | 2.63    |
| Campa (NIHS) (2011) | 1.22 (1.13, 1.32)   | 3.68    |
| Campa (VHL) (2011) | 1.25 (0.77, 1.45)   | 1.61    |
| Campa (MEC) (2011) | 1.22 (0.90, 1.50)   | 1.00    |
| He (2012)      | 1.12 (0.96, 1.19)   | 4.60    |
| Fletcher (2011) | 1.16 (1.11, 1.22)   | 5.15    |
| Stacey (Holand) (2007) | 1.20 (1.13, 1.28)   | 4.15    |
| Stacey (Sweden) (2007) | 1.22 (0.99, 1.37)   | 2.38    |
| Stacey (Spain) (2007) | 1.21 (0.63, 1.42)   | 1.46    |
| Stacey (Holland) (2007) | 1.16 (0.91, 1.43)   | 1.77    |
| Stacey (Latinaos) (2007) | 1.21 (0.99, 1.47)   | 1.06    |
| Herbst (2012)  | 1.11 (0.94, 1.18)   | 4.38    |
| Reeves (2010)  | 1.16 (1.11, 1.21)   | 5.36    |
| Li (Swedish) (2011) | 1.19 (0.94, 1.35)   | 1.99    |
| Li (Finnish) (2011) | 1.14 (0.90, 1.30)   | 1.97    |
| Slattary (2011) | 1.06 (0.95, 1.19)   | 2.46    |
| Slattary (2011) | 1.26 (0.77, 1.68)   | 1.46    |
| Mine (2000)    | 1.15 (1.13, 1.16)   | 6.32    |
| Antoniou (2009) | 1.06 (0.60, 1.12)   | 4.56    |
| Antoniou (2009) | 1.07 (0.99, 1.15)   | 3.74    |
| Bakhlopis Sloan (2010) | 1.07 (0.94, 1.20)   | 2.18    |
| Stevens (2011) | 1.04 (0.67, 1.11)   | 4.12    |
| Hennemiti (2010) | 1.15 (0.64, 1.28)   | 2.69    |
| Tenaska (2011) | 1.12 (0.95, 1.28)   | 2.03    |
| Subtotal (I² = 39.1%, p = 0.023) | 1.14 (1.12, 1.17)   | 78.10   |
| East Asian    |                     |         |
| Campa (MEC) (2011) | 1.10 (0.85, 1.41)   | 0.66    |
| Zheng (2010)   | 1.03 (0.92, 1.16)   | 2.34    |
| Dai (T3) (2012) | 1.28 (0.85, 1.56)   | 1.04    |
| Dai (IVS) (2012) | 1.18 (0.86, 1.54)   | 0.97    |
| Kim (2012)     | 1.11 (0.96, 1.28)   | 1.73    |
| Suata (2012)   | 0.98 (0.78, 1.23)   | 0.86    |
| Mine (2009)    | 1.09 (0.96, 1.24)   | 1.99    |
| Lin (2012)     | 2.04 (1.25, 2.87)   | 0.07    |
| Jang (2011)    | 1.26 (1.05, 1.67)   | 0.54    |
| Subtotal (I² = 29.6%, p = 0.182) | 1.12 (1.03, 1.21)   | 10.19   |
| African       |                     |         |
| Campa (MEC) (2011) | 1.08 (0.86, 1.31)   | 0.92    |
| Hsu (2012)     | 0.99 (0.97, 1.12)   | 2.08    |
| Zheng (OCSP) (2009) | 1.08 (0.90, 1.28)   | 1.25    |
| Zheng (NIHS) (2009) | 1.52 (1.20, 2.28)   | 0.42    |
| Shaw (2012)    | 1.13 (0.95, 1.36)   | 1.18    |
| Chen (2011)    | 1.12 (0.93, 1.31)   | 3.53    |
| Hutter (2011)  | 0.93 (0.79, 1.12)   | 1.28    |
| Subtotal (I² = 39.8%, p = 0.126) | 1.07 (0.99, 1.14)   | 10.68   |
| Other         |                     |         |
| Campa (MEC) (2011) | 0.84 (0.61, 1.17)   | 0.41    |
| Riwka (2013)   | 1.80 (1.38, 2.35)   | 0.81    |
| Subtotal (I² = 91.8%, p = 0.000) | 1.24 (0.59, 2.61)   | 1.02    |
| Overall       |                     |         |
| (I² = 47.6%, p = 0.000) | 1.14 (1.11, 1.16)   | 100.00  |

Figure 1. Forest plot from the meta-analysis of breast cancer risk and 2q35-rs13387042 polymorphism.
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factor, the 2q35-rs13387042 polymorphism has a very small but detectable effect on susceptibility to breast cancer. This could be regarded simply as a weak genetic effect that has an additive effect when combined with other susceptibility loci.

Compared with the previous meta-analysis [50], the present study is much larger, with almost sixty times as many cases as the earlier meta-analysis. In addition, we also performed analyses to test for differences in the associations of the polymorphism with breast cancer risk with respect to different hormone receptor status. Furthermore, we explored potential sources of heterogeneity across studies.

Limitations also inevitably existed in this meta-analysis. First, our meta-analysis is based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available, which would allow for an adjustment estimate. To be made, however, this approach requires the authors of all of the published studies to share their data. Second, no statistically significant association between the polymorphism and breast cancer appeared in other ethnic populations in racial subgroup analysis. However, the other ethnic population reports in the subgroup analysis include a mixture of populations from very distant countries, so the result must be interpreted with caution.
Finally, the subgroup meta-analyses considering interactions between rs13387042 polymorphism and hormone receptor status, as well as tumor invasiveness were performed on the basis of a fraction of all the possible data to be pooled, so selection bias may have occurred and our results may be overinflated. Nevertheless, the total number of subjects included in this part of the analysis comprises the largest sample size so far.

Despite these limitations, this meta-analysis suggests that 2q35-rs13387042 polymorphism was significantly associated with increased risk of breast cancer, particularly in East Asian and white populations. As studies among other ethnic populations are currently limited, further studies including a wider spectrum of subjects to investigate the role of this variant in other populations will be needed.

Supporting Information

Figure S1 Flow chart of literature search.

(TIF)

Table S1 Meta-analysis of the 2q35-rs13387042 polymorphism on breast cancer risk using co-dominant model.

(DOCX)

Author Contributions

Conceived and designed the experiments: TH JH QYW JS. Performed the experiments: TH JH WLL QQY KLN. Analyzed the data: TH JH WLL QQY KLN. Contributed reagents/materials/analysis tools: WLL QQY KLN. Wrote the paper: TH JH QYW JS.

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