Abstract

Objectives: We carried out a meta-analysis focusing on the relationship between length of AIB1 gene poly-Q repeat domain as a modifier of breast cancer (BC) susceptibility in patients with BRCA1 and BRCA2 mutation carriers.

Data sources: We searched MEDLINE and EMBASE for all medical literature published until February, 2012.

Study Eligibility criteria: Studies were included in the meta-analysis if they met all the predetermined criteria, such as: (a) case-control or cohort studies; (b) the primary outcome was clearly defined as BC; (c) the exposure of interest measured was AIB1 polyglutamine repeat length genotype; (d) provided relative risk (RR) or odds ratio (OR) estimates and their 95% confidence intervals (CIs).

Synthesis methods: Two of the authors independently evaluated the quality of the studies included and extracted the data. Meta-analyses were performed for case-control and cohort studies separately. Heterogeneity was examined and the publication bias was assessed with a funnel plot for asymmetry.

Result: 7 studies met our predetermined inclusion criteria and were included in the meta-analysis. Overall quality ratings of the studies varied from 0.36 to 0.77, with a median of 0.5. The overall RR estimates of 29/29 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2, were always greater than 1.00; however, this effect was not statistically significant. In the meta-analysis of studies reporting the effect of 28/28 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2, the overall RR decreased below 1.00; however, this effect was not statistically significant. Similar estimates were shown for at least 1 allele of ≤26 repeats.

Conclusions: Genotypes of AIB1 polyglutamine polymorphism analyzed do not appear to be associated to a modified risk of BC development in BRCA1 and BRCA2 mutation carriers. Future research on length of poly-Q repeat domain and BC susceptibility should be discouraged and more promising potential sources of penetrance variation among BRCA1 and BRCA2 mutation carriers should be investigated.

Introduction

Hereditary breast cancer (BC) is characterized by a high degree of clinical and genetic heterogeneity. The inheritance of BC susceptibility in families has led to the identification of two major BC susceptibility genes, BRCA1 and BRCA2 [1–3]. Inherited mutations in BRCA1 confer lifetime risks of breast cancer of 70% to 80% [4,5]. The corresponding risk for BRCA2 mutation carriers is estimated to be 50–60% [6–8]. The pathogenic role of nonsense and frame shift mutations is well recognized in breast carcinogenesis, while the impact of missense mutations is still to be defined [9–14].

Several studies have reported associations between common polymorphisms in candidate gene studies and the risk of breast or ovarian cancer for mutation carriers, but normally these associations have not been replicated in subsequent studies [15–17]. Genes coding for proteins involved in steroid hormone signaling have been examined as risk-modifier candidates. Steroid hormone receptors and their co-activators, such as AIB1, are prime candidate modifiers.

The AIB1 gene coding for a member of steroid hormone receptor coactivator from the SRC1 family of transcriptional co-activators is involved in the control of estrogen-dependent transcription [18,19]. AIB1, also called SRC3, together with...
other co-activators and co-repressor proteins is implicated in estrogen signaling pathway and estrogen regulated tumor progression. Within the carboxyl-terminal region of AIB1 lays a polymorphic stretch of glutamine residues (poly-Q) [20] and it has been proposed that AIB1 poly Q domain may directly influence transactivation of estrogen receptor (ER) and thus susceptibility to BC.

Several studies have been conducted in order to analyze length of poly-Q repeat domain as a modifier of BC susceptibility both in patients with sporadic BC [21,22], and BRCA 1/2 mutation carriers [23–29], and the results are yet controversial and inconclusive. Since most studies had relatively small sample sizes and single studies with enough subjects were currently lacking, we may join pieces of evidence from published literature for a meta-analysis. Moreover, this topic has been analyzed in a previous meta-analysis, that demonstrated an increased breast cancer risk in BRCA1/2 mutation carriers for individuals with both alleles C29 polyglutamine repeat [30].

The overarching goal of cancer risk assessment is to indicate cancer risk management recommendations taking into account potential factors that may influence penetrance. Methods to calculate risk make use of health history information, risk factor and family history data in combination with emerging biologic and genetic/genomic evidence to establish predictions. In this study, we carried out a meta-analysis focusing on the relationship between length of poly-Q repeat domain as a modifier of BC susceptibility in patients with BRCA1/2 mutation carriers to provide a basis for more evidence-based counselling and decision making.

Materials and Methods

Search Strategy for Identification of Studies

We sought to identify all epidemiological studies that investigated the association between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers. Studies were identified through electronic databases search and scanning the reference lists of the eligible articles. No restrictions on language were imposed. We searched MEDLINE, and EMBASE for all medical literature published until February, 2012. The search was performed by consecutively entering “BRCA1”, “BRCA2” “mutation”, “mutations”, “carrier”, “carriers”, “breast” “cancer”, and “AIB1”, “NCOA3”, “SRC3” as both medical subject heading terms and text words.

Inclusion Criteria

Two of the authors were involved in the selection of studies for the review and discrepancies were resolved by discussion after retrieving the full text of articles in question. Studies were included in the meta-analysis if they met all of the following criteria: (a) report original data from case-control or cohort studies; (b) the primary outcome was clearly defined as BC; (c) the exposure of interest measured was AIB1 polyglutamine repeat length genotype (1 allele ≥26, both alleles ≥28, both alleles ≥29); (d) provided relative risk (RR) or odds ratio (OR) estimates and their 95% confidence intervals (CIs) or sufficient data to calculate these estimates; (e) published through February, 2012. If a study appeared in more than one article, data from the most recent publication were used for statistical analysis. We excluded studies including also BRCA1/2 non carriers; letters, abstracts, theses,
| Authors                      | Country                     | Study type   | No. of cases/ exposed | No. of control/not exposed | Variables of adjustment | Mutation carriers | AIB1 polyglutamine repeat length genotype groups | Crude (c) or adjusted (a) RR/OR estimate (95% CI) | Quality score |
|------------------------------|-----------------------------|--------------|-----------------------|---------------------------|-------------------------|------------------|---------------------------------|---------------------------------|---------------|
| Rebbeck et al., 2001 [23]    | USA, Canada                 | Case-control | 278                   | 170                       | Age, year of birth, age at menarche, parity, age at first live birth, smoking status | BRCA1/2           | 1 allele ≤26                  | 0.64 (0.41–1.00)                    | 0.64           |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥28               | 1.59 (1.03–2.47)*                  |               |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 2.85 (1.64–4.96)*                  |               |
| Kadouri et al., 2004 [24]    | Israel, UK                  | Cohort       | 195                   | 116                       | None                   | BRCA1/2           | 1 allele ≤26                  | 0.87 (0.7–1.09)*                    | 0.58          |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥28               | 1.15 (0.92–1.44)                   |               |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 1.21 (1.01–1.46)                   |               |
| Hughes et al., 2005 [25]     | France, Greece, USA Cohort  | Cohort       | 642                   | 449                       | Year of birth, parity  | BRCA1/2           | both alleles ≥28               | 0.68 (0.75–1.04)                    | 0.5           |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 1.06 (0.88–1.27)                   |               |
|                              |                             |              |                       |                           |                         |                  | BRCA1                         | 1.02 (0.83–1.26)                   |               |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 1.02 (0.81–1.28)                   |               |
|                              |                             |              |                       |                           |                         |                  | BRCA                          | 0.67 (0.51–0.88)                   |               |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 1.16 (0.86–1.57)                   |               |
| Spurdle et al., 2006 [26]    | UK, Australia, North America, Quebec | Cohort | 598                   | 492                       | Year of birth, age at menarche, parity, oral contraceptive use, ethnicity | BRCA1             | both alleles ≥28               | 0.76 (0.59–0.97)*                    | 0.5           |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 0.95 (0.73–1.24)*                  |               |
| Colilla et al., 2006 [27]    | USA, Canada                 | Cohort       | 176                   | 1407                      | Year of birth, age at menarche, parity, age at first live birth, menopausal status, height, smoking status, oral contraceptive use, ethnicity | BRCA1             | 1 allele ≥26                  | 1.0 (0.8–1.26)                      | 0.42          |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥28               | 1.0 (0.88–1.13)*                   |               |
|                              |                             |              |                       |                           |                         |                  | both alleles ≥29               | 1.05 (0.84–1.33)*                  |               |
ecological studies, and conference proceedings; and studies carried out in non-humans.

Assessment of Study Quality

Two of the authors independently evaluated the quality of the studies included using a modified scoring system that was created on the basis of a systematic review [31] and with reference to QUATSO [32] and STROBE statement for observational studies [33]. Each article was read and scored for quality, and all studies had blinded investigators, institutions, country, and journal. The readers discussed their evaluation, and when discrepancies occurred they were resolved by consensus or, finally, by a third author. The list comprised items felt to be important for the quality of each observational study, including the method for selecting study participants, the adjustment for confounding variables, the method for measuring study variable and design-specific sources of bias, the data analysis, and conflict of interest. The score was calculated as the percentage of applicable quality criteria that were met in each study and a study could range from 0% (none of the quality criterion was met) to 100% (all the quality criteria were met). Studies achieving 67% or more in the score will be regarded as “good” quality; 34–66% “fair”; and, below 33% “poor”. To avoid selection bias, no study was rejected because of these quality criteria.

Data Extraction

All data from the studies were independently extracted by two of the authors using a designed form. The accuracy of the extracted data was checked by a third reviewer. The following characteristics were recorded from each study: (a) first author’s name, year of publication, and country of the population; (b) study design; (c) number of subjects; (d) confounding factors for matching or adjustment; (e) methods used for collection of data on exposure; (g) RR or OR of BC associated with AIB1 polyglutamine repeat length genotype and the corresponding 95% CI in each subgroup. For the published results of each of the selected studies, data were extracted to allow the calculation of both unadjusted and adjusted ORs with 95% CIs to estimate the association between AIB1 polyglutamine repeat length genotype and the risk of BC.

Meta-analyses

We planned to analyse case-control and cohort studies separately. The effect on risk for BC was calculated for certain AIB1 polyglutamine repeat length genotype in BRCA1/2 carriers. The analysis was repeated using results for BRCA1 and BRCA2 carriers for those studies where this result was available. Whenever possible, combined risk estimates were calculated by using the risk estimates that reflected the greatest degree of control for other reproductive risk factors (RR or OR adjusted for confounding factors). Heterogeneity among the studies was examined using the method developed by DerSimonian & Laird by calculating the between-study variation based on the Q statistic [34]. We considered that there was statistically significant heterogeneity when p value was below 0.1 among the results of the included studies. In cases with heterogeneity, we applied random-effects models as opposed to fixed-effect models because they include both within-study sampling error (variance) and between-study variation in the assessment of the uncertainty (CI) of the results of a meta-analysis.

Finally, the presence of publication bias was assessed with a funnel plot for asymmetry, a scatter plot of individual studies that relates the magnitude of the treatment effect against a measure of Table 1. Cont.

| Authors | Country |mutation carriers | No. of control/ not exposed | No. of cases/ exposed | Variables of adjustment | AIB1 polyglutamine repeat length genotype groups | Crude (c) or adjusted (a) OR estimate | Quality score |
|---------|---------|-------------------|-----------------------------|-----------------------|------------------------|-----------------------------------------------|--------------------------------------|--------------|
| Jakubowska et al., 2010 [28] | Poland | BRCA1 | 319 | 290 | Year of birth, age at menarche, parity, age at first live birth, breastfeeding, BHR*, smoking status, oral contraceptive use | both alleles ≥28 | 0.87 (0.54–1.41) | 0.77 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | BRCA1/2 | 0.96 (0.85–1.09) | 0.36 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | BRCA1/2 | 0.96 (0.85–1.09) | 0.36 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | Both alleles | 0.96 (0.85–1.09) | 0.36 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | Both alleles | 0.96 (0.85–1.09) | 0.36 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | Both alleles | 0.96 (0.85–1.09) | 0.36 |
| Kleibl et al., 2011 [29] | Czech Republic | BRCA1 | 211 | 32 | None | Both alleles | 0.96 (0.85–1.09) | 0.36 |

*BHR: body mass index.
its precision [35], using for formal statistical testing an adjusted rank correlation test and a regression asymmetry test [36,37].

All analyses were performed using Stata statistical software (version 11) [38].

**Results**

**Study Characteristics**

We identified a total of 308 potentially relevant studies that described the association between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers, but on obtaining and reading the articles, our predetermined inclusion criteria were met only by 7 studies that were included in the meta-analysis [23–29]. A list of the excluded papers is available from the authors. Articles were excluded from the analyses for any one of the following reasons: (1) review paper; (2) letters or editorial; (3) laboratory study; (4) survey study; (5) no sufficient published data for determining an estimator of RR (OR) or a variance; (6) results on BC were mixed with BRCA1/2 mutation carriers and non-carriers (Figure 1). The overall agreement among reviewers on selection of the studies was excellent, since it was higher than 99%.

The summary characteristics of all studies included in the meta-analysis are described in Table 1. The sample size of the 7 included studies (5 cohort and 2 case-controls) varied between 57 and 642 for exposed and between 2 and 1,407 for non-exposed in cohort studies, respectively, and between 278 and 319 for cases and between 170 and 290 for controls in case-control studies, respectively. The studies were geographically heterogeneous: 5 studies involved European samples, 4 studies were conducted in North America, 1 in Israel and 1 in Australia. To give an indication of the actual RR/OR found in the studies, we also show for each study the relative risks for the group with the different exposure in that study. Four studies for AIB1 polyglutamine repeat length genotype (1 allele $\leq 26$, both alleles $\geq 28$, both alleles $\geq 29$) reported adjusted RR/ORs [25,26,28,29]; two studies provided sufficient data to calculate a crude RR [24,27], and the paper by Rebbeck and colleagues [23] reported adjusted OR for both alleles $\geq 28$ and $\geq 29$ length genotype groups, and sufficient data to calculate a crude OR for 1 allele $\leq 26$ length genotype group.

| Quality scoring item                                | % of studies complying* |
|-----------------------------------------------------|--------------------------|
| **Case-control studies**                            |                          |
| Cases either randomly selected or selected to include all cases in a specific population | 100                      |
| Cases identified without knowledge of exposure status | 100                      |
| Controls drawn from the same population of cases    | 100                      |
| No known association between control status and exposure | 100                      |
| **Cohort studies**                                  |                          |
| Comparison/Description of persons who did and did not participate | 20                       |
| Comparison of who were and were not lost to follow-up | 0                       |
| Exposed/non-exposed subjects identified without knowledge of disease status | 40                       |
| **All studies**                                     |                          |
| Any response rate was reported                      | 0                        |
| An estimation of the sample size was made           | 14.3                     |
| **Adjustment or matching for confounders**          |                          |
| Year of birth                                       | 71.4                     |
| Age at menarche                                     | 57.1                     |
| Parity                                              | 71.4                     |
| Age at first live birth                             | 42.9                     |
| Smoking status                                      | 42.9                     |
| Oral contraceptive use                              | 42.9                     |
| Ethnicity                                           | 28.6                     |
| Menopausal status                                   | 14.3                     |
| Height                                              | 14.3                     |
| Breastfeeding                                       | 14.3                     |
| Body mass index (BMI)                               | 14.3                     |
| **Statistical methods**                             |                          |
| Basic characteristics listed                        | 14.3                     |
| Losses of participants, missing data or other design defects were adequately treated | 0                        |
| Precise $p$ values and/or confidence interval and/or power given | 100                      |
| **Conflict of interest declared**                   | 42.9                     |

*If compliance is not specifically indicated in the text, non compliance is assumed.

doi:10.1371/journal.pone.0057781.t002

**Table 2.** Items used in quality scoring for studies of the association between polymorphic repeat length in the AIB1 gene and breast cancer risk in BRCA1 and BRCA2 mutation carriers.
Three papers provided information on BRCA1 and BRCA2 carriers separately and combined, two papers only on BRCA1 carriers, one paper on BRCA1 and BRCA2 carriers separately, and another paper only the combined data. Two studies did not use statistical adjustment for any potential confounding factors. Five papers made some adjustments for potential confounding factors; only two, however, adjusted for year of birth, age at menarche, parity, age at first live birth and oral contraceptive use. Studies using both polymerase chain reaction (PCR)-amplified and non-amplified genotyping methods were included. There were no restrictions on PCR primers’ utilization.

Data Quality
The overall agreement among reviewers on evaluation of the quality of the studies was higher than 85% and differences were resolved by a third reviewer.

The potential risk of bias associated with various aspects of study design is described in Table 2 that summarizes the quality of the epidemiological studies included in the meta-analysis. Overall quality ratings of the studies varied from 0.36 to 0.77, with a median of 0.5. In all studies cases and controls were identified without knowledge of exposure status, controls were drawn from the same population of cases and basic sample characteristics were presented. All cohort studies retrospectively ascertained cohort and in 60% of them it was not specifically indicated in the text that exposed/non-exposed subjects were identified without knowledge of disease status. The study of Rebbeck and colleagues [23] generated a nested case-control sample using an incidence density sampling design. None of the studies specified cancer diagnosis criteria although diseases like BC are subject to relatively little misclassification (false negatives are unlikely given the severity of the disease, and false positives are unlikely given the medical scrutiny of suspected cases).

The extent of adjustment for potential confounding factors in the relationship between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers varied across studies. 71.4% of studies adjusted for year of birth and parity, 57.1% for age at menarche, but 14.3% for the menopausal status, height, breastfeeding and body mass index. Only 2 studies presented adjusted OR for ethnicity. Information bias associated with failure to consider ethnicity as a confounding variable may have been a problem in the study of Kadouri and colleagues [24] that assessed the effect of the polyglutamine repeat polymorphism in the AIB1 gene on BC risk in BRCA1 and BRCA2 mutation carriers, mainly of Ashkenazi origin. No studies reported any response rate and adequately treated losses of participants, missing data or other design defects. Three studies declared conflict of interest.

Meta-analysis
When all extracted data were pooled, 5,980, 6,589 and 3,138 patients were eligible for analysis on 29/29 poly-Q repeats, 28/28 poly-Q repeats and at least 1 allele of ≤26 repeats, respectively. The objectives of all available studies were to analyze the effect of AIB1 poly-Q domain polymorphism genotypes and BC onset among BRCA1/2 mutation carriers. Figure 2 shows data of meta-analysis exploring the effect of 29/29 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2 mutation carriers. Figure 2. Meta-analysis exploring the effect of 29/29 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2 mutation carriers. doi:10.1371/journal.pone.0057781.g002
Figure 3. Meta-analysis exploring the effect of 28/28 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2 mutation carriers. doi:10.1371/journal.pone.0057781.g003
Figure 4. Meta-analysis exploring the effect of 26/26 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2 mutation carriers. doi:10.1371/journal.pone.0057781.g004
than 1.00, indicating a potential effect of 29/29 poly-Q repeats on BC onset, however, this effect was not statistically significant.

In the meta-analysis of studies reporting the effect of 28/28 poly-Q repeats on risk of BC in BRCA1/2, BRCA1, and BRCA2, the overall RR decreased below 1.00, however, this effect was not statistically significant (Figure 3). The pooled RR estimate for at least 1 allele of ≤26 repeats performed in BRCA1/2, BRCA1, and BRCA2 mutation carriers were similar to the 28/28 poly-Q repeats (Figure 4). The Q statistic test of homogeneity found a statistically significant heterogeneity across the studies on 28/28 poly-Q repeats; indeed, the results for BRCA1 (Q = 7.83, df = 4, \(p = 0.098\)) and for BRCA2 carriers (Q = 9.29, df = 3, \(p = 0.026\)) were heterogeneous.

A separate meta-analysis was performed for the two case-control studies reporting data on 28/28 AIB1 poly-Q domain in BRCA1/2 and BRCA1 mutation carriers, respectively. The overall OR resulting from those studies was greater than 1.00, however, this effect was not statistically significant (data not shown).

Funnel plots displaying RRs of the individual study versus the reciprocal of their standard errors did not show any substantial asymmetry in studies exploring the effect of 29/29 and 28/28 AIB1 poly-Q domain on risk of BC in BRCA1/2 \(p = 0.117\), Begg & Mazumdar adjusted rank correlation test, \(p = 0.405\), Egger et al. regression asymmetry test; \(p = 0.766\), Begg & Mazumdar adjusted rank correlation test, \(p = 0.602\), Egger et al. regression asymmetry test, respectively. Analogously, no significant funnel plot asymmetry was observed for studies exploring the effect of at least 1 allele of ≤26 repeats on risk of BC in BRCA1/2, using the test of Egger et al. \(p = 0.372\), as well as the test of Begg & Mazumdar \(p = 0.317\).

**Discussion**

Several studies have reported associations between common polymorphisms in candidate genes studies and the risk of BC for mutation carriers. Steroid hormone receptors and their co-activators, such as AIB1, have been prime examined as risk modifier candidates. A few studies have so investigated the genetic contribution of the AIB1 gene polyglutamine repeat length as a risk factor influencing BC onset in BRCA1/2 carriers with contradictory results. Hence, we conducted a meta-analysis of observational studies examining the association between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers. Despite AIB1 is considered to be only a low penetrant BC modifier, its clinical role could be potentially considerable because the population frequency of AIB1 genotype coding for 28/28 poly-Q repeats is substantially higher (10%) compared to the majority of other low penetrant BC alleles.

Meta-analysis performed did not reveal any association between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers. The number of analyzed BRCA2 mutation carriers in the included studies is limited, but the overall RR estimates of the meta-analyses of all AIB1 poly-Q domain polymorphism genotypes were always not statistically significant. Moreover, we also performed separate meta-analyses for BRCA1 and BRCA2 mutation carriers since we believe that pooling of BRCA1 and BRCA2 mutation carriers for analyses of AIB1 poly-Q repeat polymorphism could be disputable considering the substantial differences in effects of AIB1 polymorphism in these groups and also assuming the diverse histopathological and molecular characteristic of breast tumors in BRCA1 and BRCA2 carriers.

The initial studies of Rebbeck et al. [23] and Kadouri et al. [24] reported the positive correlation between BC risk and increased lengths in AIB1 poly-Q repeat notably in BRCA1 mutation carriers. Later studies failed to confirm the association of AIB1 poly-Q repeat length polymorphism with BC risk in BRCA1/2 mutation carriers. A more recent study [29] indicated that carriers of the AIB1 genotype coding for 28/28 poly-Q repeats with a mutation in the BRCA1 gene had reduced BC risk compared to BRCA1 mutation carriers with other AIB1 genotypes, confirming findings from a previous study [27]. Moreover, the authors observed that AIB1 28/28 genotype strongly increased the BC risk only in carriers of BRCA2 mutation localized in exon 11. Studies that performed additional analysis evaluating the BC risk in women carrying at least 1 allele of ≤26 repeats in the polymorphic region of AIB1 found no significant differences on risk of BC in BRCA1/2 mutation carriers. Only the study by Kadouri et al. indicated a significant reduction of BC risk in carriers of BRCA1 mutations with the shorter polyglutamine chain of AIB1 gene [24].

A recent meta-analysis presented subgroup analyses considering BRCA1 and BRCA2 mutation carriers and found increased breast cancer risk for women with both alleles ≥29 repeat [30]. The comparison with our results is difficult, regardless of the differences in the inclusion criteria used. In particular, the meta-analysis by Zhang et al. involved 2 of the cohort [24,29] and 2 of the case-control [23,29] studies included in ours and 1 case-control study [22] that we excluded because reported the estimates of BC risk and allele frequency only among cases carrying a germline mutation in BRCA1 and BRCA2 and not for controls. The objective of the present meta-analysis was to combine all available information, which yields an increase in power, to generate an integrated result used to provide evidence for genetic counselling strategy in specific subgroups of population with an increased risk of BC and to design future research.

Moreover, we performed separate meta-analyses for cohort and case-control studies to analyze the association between AIB1 polymorphisms and BC susceptibility in BRCA1 and BRCA2 mutation carriers.

On the other hand, differences in the associations of the modifying polymorphisms with breast cancer risk for BRCA1 and BRCA2 mutation carriers are likely to reflect differences in the biology of tumor development in these two groups of women at high risk of BC.

In this meta-analysis the quality of the observational studies was fair. The evaluation of the quality of the studies in a meta-analysis may contribute to point out limitations in published studies and to suggest ways to improve the methodology of studies in further research. For example, only three studies declared conflict of interest and, since funding source has been shown to be an important source of heterogeneity, the sponsoring organization should be disclosed, so any effect on analysis could be examined. Indeed, it is reported that meta-analyses without (or undeclared) financial support are of inferior quality than meta-analyses with profit and non-profit support [39].

The value of the current meta-analysis compensates for the individual lack of precision of most studies, a problem alleviated by pooling. As no significant results could lead to incorrectly accept a false null hypothesis, making a type II error of omission, we performed a post-hoc power calculation to examine whether the lack of adequate power accounts for the blurring of associations. The post-hoc power calculation showed that our set of studies had sufficient statistical power (0.85) to detect a significant difference between the effect size in the two groups of \(d = 0.14\).
Strengths and Limitations of the Study

The main strengths of our study include the rigorous methods employed to identify studies and assessment of potential risk of bias. The lack of association between certain polymorphic repeat length in the AIB1 gene and BC risk in BRCA1 and BRCA2 mutation carriers was robust to a number of subgroups. We did not observe any evidence of publication bias in the studies included in our review, which decreases the likelihood that our findings were related to our method of selecting articles. Moreover, the amount of heterogeneity among studies seems to be low and the between-studies dispersion seems less than would be expected by chance.

The strengths of the present meta-analysis also include absence of restriction to studies published in English, since language restriction could introduce bias in the results of the meta-analysis [40,41].

Possible limitations of all meta-analyses of observational studies are related to absence of a “gold standard” instrument for the quality assessment and, although several assessment scales and checklists have been used [42–44] none of them has been fully validated. Moreover, one of the most well-known proposed scoring system, the Newcastle-Ottawa-Scale (NOS) by Wells [45] et al. has recently been considered of unknown validity at best, or including quality items that are even invalid [46]. Therefore, we preferred to propose a modified scoring system that, with reference to QUATSO [32] and STROBE statement for observational studies [33], appeared to us more adequate to address the specific methodological issues related to our study.

The present meta-analysis include poor methodological quality of the studies on which the analysis is based. Many of the studies included in our review were at some potential risk of bias from certain aspects of study design and the potential biases inherent in all observational studies may have contributed to the observed findings. It has been argued that since meta-analysis of observational studies may produce very precise, but spurious results, statistical combination of these data should not be the prominent component. Therefore, taking the quality of studies into account in a meta-analysis has the potential to enhance the validity of a meta-analysis because quality is implicitly a measure of validity [47].

Moreover, the evaluation of the quality of the studies in a meta-analysis may contribute to point out limitations in published studies and suggest ways to improve the methodology of studies in further research. In this meta-analysis the quality of the observational studies, in particular cohort studies, was scant with regard to the various methodological aspects of the study design (for example, comparison of who were and were not to follow-up, comparison or description of persons who did and did not participate, knowledge of disease status after exposed/non-exposed subjects were identified). Other shortcomings were related to the response rate reporting and adjustment for confounders. Many but not all of the studies adjusted for potential confounding factors, although not all potential confounders were adjusted for in every study, and this might have had an impact on our overall dataset. In our meta-analysis we included the most fully adjusted hazard ratio presented in the articles. Indeed, only 2 of the 7 included studies adjusted for what we considered in our quality assessment tool as essential confounders (year of birth, age at menarche, parity, age at first live birth, smoking status, oral contraceptive use).

In conclusion, on the basis of epidemiological evidence, genotypes of AIB1 polyglutamine polymorphism—analyzed in categories according to cut-points 1 allele ≤26, both alleles ≥28 and ≥29—do not appear to be associated to a modified risk of BC development in BRCA1 and BRCA2 mutation carriers. Future research on length of poly-Q repeat domain and BC susceptibility should be encouraged and more promising potential sources of penetrance variation among BRCA1 and BRCA2 mutation carriers should be investigated.

Author Contributions

Wrote the first draft of the article: AB BQ. Searched the literature and extracted the data: AB CP CD MCF. Guarantors for the study: FC MP. Had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: MP AB BQ CP MF CDL FC. Conceived and designed the experiments: AB, BQ, MP, FC. Performed the experiments: AB, CP, CD, MCF. Analyzed the data: AB, CP. Wrote the paper: MP, FC.

References

1. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 266: 66–71.
2. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, et al. (1995) Identification of the breast cancer susceptibility gene BRCA2. Nature 378: 789–792.
3. Antoniou A, Pharoah PD, Narod S, Risck HA, Eysfford JE, et al. (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 72: 1117–1130.
4. FitzGerald MG, MacDonald DJ, Kraimer M, Hoover L, O’Neil E, et al. (1996) Germ-line BRCA1 mutations in Jewish and non-Jewish women with early onset breast cancer. N Engl J Med 334: 143–149.
5. Yang Q, Sakurai T, Mori I, Yoshimura G, Nakamura M, et al. (2001) Prognostic significance of BRCA1 expression in Japanese sporadic breast carcinomas. Cancer 92: 54–60.
6. Antoniou AC, Cumming AP, Petro J, Evans DG, Laloo F, et al. (2008) The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. Br J Cancer 98: 1457–1466.
7. Berg CB, Haile RW, Borg A, Malone KE, Concannon P, et al. (2006) Variation of breast cancer risk among BRCA1/2 carriers. JAMA 299: 194–201.
8. Milne RL, Osorio A, Cajal TR, Vega A, Lliot G, et al. (2008) The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. Clin Cancer Res 14: 2861–2869.
9. Gayther SA, Warren W, Mazoyer S, Russell PA, Harrington PA, et al. (1993) Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation. Nat Genet 11: 420–423.
10. Friedman LS, Ostermeyer EA, Szabo CI, Dowell P, Lynch ED, et al. (1994) Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families. Nat Genet 8: 399–404.
11. Quaresima B, Fanelli MG, Baudi F, Cruciliano T, Di Sanzo M, et al. (2006) Missense mutations of BRCA1 gene affect the binding with p53 both in vitro and in vivo. Oncol Rep 11: 811–815.
12. Cruciliano T, Quaresima B, Gaspari M, Fanelli MC, Romeo F, et al. (2007) Specific changes in the protocin pattern produced by the BRCA1–1841Asn missense mutation. Int J Biochem Cell Biol 39: 220–226.
13. Quaresima B, Romeo F, Fanelli MC, Di Sanzo M, Liu CG, et al. (2008) BRCA1 5083del19 mutant allele selectively up-regulates periostin expression in vitro and in vivo. Clin Cancer Res 14: 6797–6803.
14. Quaresima B, Fanelli MG, Baudi F, Cruciliano T, Cudia G, et al. (2006) In vitro analysis of genomic instability triggered by BRCA1 missense mutations. Hum Mutat 27: 715.
15. Spurdle AB, Antoniou AC, Duffy DL, Pandeya N, Kelemen L, et al. (2005) The androgen receptor CAG repeat polymorphism and modification of breast cancer risk in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res 7: R176–183.
16. Osorio A, Mihay RL, Alonso R, Pita G, Peterlongo P, et al. (2011) Evaluation of the XRCC1 gene a saphenotypic modifier in BRCA1/2 mutation carriers. Results from the consortium of investigators of modifiers of BRCA1/2. Br J Cancer 104: 1356–1361.
17. Sinilnikova OM, Antoniou AC, Simard J, Healey S, Leone M, et al. (2009) The TP53 Arg72-Pro and MDM2309G26, both alleles $ do not appear to be associated to a modified risk of BC.
AIB1 Gene and Breast Cancer Risk: A Meta-Analysis

19. Bautista S, Valles H, Walker RL, Anzick S, Zeilinger R, et al. (1998) In breast cancer, amplification of the steroid receptor coactivator gene AIB1 is correlated with estrogen and progesterone receptor positivity. Clin Cancer Res 4: 2925–2929.

20. Shirazi SK, Beber MA, Coetzee GA (1990) Polymorphic exonic CAG microsatellites in the gene amplified in breast cancer (AIB1) gene. Clin Genet 54: 102–103.

21. Haiman CA, Hankinson SE, Spiegelman D, Colditz GA, Willett WC, et al. (2000) Polymorphic repeat in AIB1 does not alter breast cancer risk. Breast Cancer Res 2: 373–383.

22. Montgomery KG, Chang JH, Gertig DM, Dite GS, McCredie MR, et al. (2005) The AIB1 glutamine repeat polymorphism is not associated with risk of breast cancer before age 40 years in Australian women. Breast Cancer Res 7: R353–R356.

23. Rebbeck TR, Wang Y, Kantoff PW, Kritihivis K, Neuhausen SL, et al. (2001) Modification of BRCA1- and BRCA2-associated breast cancer risk by AIB1 genotype and reproductive history. Cancer Res 61: 5420–5424.

24. Kadouri I, Kote-Jarai Z, Easton DF, Hubert A, Hamoudi R, et al. (2000) Polyglutamine repeat length in the AIB1 gene modifies breast cancer susceptibility in BRCA1 carriers. Int J Cancer 108: 399–403.

25. Hughes DJ, Ginolhac SM, Couper I, Barihoumi L, Gaborieau V, et al. (2005) Breast cancer risk in BRCA1 and BRCA2 mutation carriers and polyglutamine repeat length in the AIB1 gene. Int J Cancer 117: 230–233.

26. Spurdle AB, Antoniou AC, Kelemen L, Holland H, Peock S, et al. (2006) The AIB1 polyglutamine repeat does not modify breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Epidemiol Biomarkers Prev 15: 76–79.

27. Colilla S, Kantoff PW, Neuhausen SL, Godwin AK, Daly MB, et al. (2006) The joint effect of smoking and AIB1 on breast cancer risk in BRCA1 mutation carriers. Carcinogenesis 27: 599–605.

28. Jakubowska A, Gronwald J, Mienkiszak J, Gorski B, Huzarski T, et al. (2010) BRCA1-associated breast and ovarian cancer risks in Poland: no association with commonly studied polymorphisms. Breast Cancer Res Treat 119: 291–211.

29. Kleibl Z, Hazanek O, Kormunda S, Novotna J, Foretova L, et al. (2011) The AIB1 gene polyglutamine repeat length polymorphism and the risk of breast cancer development. J Cancer Res Clin Oncol 137: 331–338.

30. Zhang Y, Huang M, Zhu Z (2012) AIB1 polymorphisms with breast cancer susceptibility: a pooled analysis of variation in BRCA1/2 mutation carriers and non-carriers. Mol Biol Rep 39: 6881–6886.

31. Sanderson S, Tatt ID, Higgins JP (2007) Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol 36: 666–676.

32. Wong WCW, Cheung CSK, Hart GJ (2008) Development of an assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. Emerg Themes Epidemiol 5: 23.

33. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, et al. (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61: 344–349.

34. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188.

35. Sterne JA, Egger M, Smith GD (2001) Investigating and dealing with publication bias and other biases in meta-analysis. BMJ 323: 101–105.

36. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088–1099.

37. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 602–606.

38. StataCorp 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP.

39. De Vito C, Manzoli L, Marszullo C, Anastasi D, Boccia A, et al. (2007) A systematic review evaluating the potential for bias and the methodological quality of meta-analyses in vaccinology. Vaccine 25: 8794–8806.

40. Moher D, Fortin P, Jadad AR, Juni P, Klassen T, et al. (1996) Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. Lancet 347: 363–366.

41. Gregoire G, Derderian F, LeLoirer J (1995) Selecting the language of the publications included in a meta-analysis: is there a tower of Babel bias? J Clin Epidemiol 48: 159–163.

42. Manzoli L, De Vito C, Marszullo C, Boccia A, Villari P (2012) Oral contraceptives and venous thromboembolism: A systematic review and meta-analysis. Drug Saf 35: 191–205.

43. Pavía M, Bianco A, Pileggi C, Angelillo IF (2000) Meta-analysis of residential exposure to radon gas and lung cancer. Bull World Health Organ 78: 733–739.

44. Pavia M, Pileggi C, Nobile CGA, Angelillo IF (2006) Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. Am J Clin Nutr 83: 1126–1134.

45. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 602–606.

46. Stang A (2010) Critical evaluation of the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603–605.

47. Laird NM, Mosteller F (1990) Some statistical methods for combining experimental results. Int J Technol Assess Health Care 6: 5–30.