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Association between *BRIP1* (*BACH1*) polymorphisms and breast cancer risk: a meta-analysis

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Abstract Inconsistency of reported associations between the *Pro919Ser* polymorphism in the *BRCA1* interacting protein 1 (*BRIP1*) gene and breast cancer prompted us to undertake a meta-analysis. Although investigated by fewer studies, we have also studied the risk associated with the two additional *BRIP1* polymorphisms, *C47G* and *G64A*, and breast cancer riskWe conducted searches of the published literature in MEDLINE through PubMed up to October 2012. Individual data on 5,122 cases and 5,735 controls from eight published case–control studies were evaluated for the *Pro919Ser* polymorphism. Accordingly, *C47G* and *G64A* polymorphisms were studied in 1,539 cases and 1,183 controls, and 667 and 782, respectively.In the overall analysis, association was lacking between the *Pro919Ser* polymorphism and breast cancer risk (odds ratio [OR] 0.98–1.02), materially unchanged when confined to subjects of European ancestry (OR 0.96–1.03) or even in the high-powered studies (OR 0.97–1.03). In the menopausal subgroups, premenopausal women followed the null pattern (OR 0.94–0.98) for the *Pro* and *Ser* allele contrasts, but not for the *Pro-Ser* genotype comparison where significant increased risk was observed (OR 1.39, $P = 0.002$). The postmenopausal women (>50 years) exhibited a range of pooled effects from protection (OR 0.83, $P = 0.11$) in the *Pro-Ser* genotype to slightly increased risk (OR 1.12–1.16, $P = 0.28$–0.42) in the *Pro* and *Ser* allele comparisons. The *G64A* polymorphism effects were essentially null (OR 0.90–0.98), but *C47G* was found to confer non-significantly increased risk under all genetic models (OR 1.27–1.40).Upon conclusion, overall summary estimates imply no associations but suggest susceptibility among carriers of the *C47G* polymorphism and *Pro-Ser* genotype in premenopausal women. The premenopausal findings and variable outcomes in postmenopausal women require more studies for confirmation.

Keywords *BRIP1* · *BACH1* · *Pro919Ser* · Breast cancer · Case–control · Meta-analysis

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Introduction

BRCA1-interacting protein 1 (*BRIP1)* or *BRCA1*-associated C-terminal helicase-1 *(BACH1*), located at chromosome 17q23, belongs to a *DEAH* helicase family. Also known as *FANCJ*, *BRIP1/BACH1* is a tumor suppressor gene identified through mutations in breast cancer and Fanconi anemia, a childhood cancer [1]. Fanconi anemia is a genetic disease (autosomal recessive or X-linked) characterized by multiple congenital abnormalities, bone marrow failure and cancer susceptibility [2]. *BRIP1* mutations were found in Fanconi anemia patients belonging to the complementation group J (*FANCJ*) [3, 4]. *BRIP1* interacts directly with *BRCA1*, mutations of which accounts for <25 % of excess familial risk for breast cancer [5]. This interaction is mediated through *BRCT* domains of *BRCA1* that is required for establishing the G2 cell-cycle checkpoint response to DNA damage [6], where *BRIP1*

contributes to *BRCA1*-associated DNA double strand break repair and homologous recombination repair function [7, 8]. *BRIP1* is thought to unwind DNA in the vicinity of the DNA damage and facilitate access of *BRCA1* to these sites [9]. It has been suggested that *BRIP1* function is required for timely arrival of *BRCA1* into DNA damage foci for normal kinetics of double strand break repair. Using *BRIP1* deficient cells, Peng et al. [9] provide direct evidence for involvement of *BRIP1* in DNA repair as well as for localizing *BRCA1*.

Evidence suggests the presence of an association of the *BRIP1 Pro919Ser* polymorphism (dbSNP ID: rs4986764) with breast cancer [10] although other evidence point to its absence [11, 12]. The *Ser* allele variant in *Pro919Ser* has recently been associated with an increased breast cancer risk in a kin-cohort study [13]. However, a SNP tagging approach as well as a case–control study [12] found no associations of this polymorphism with this disease [14]. Other approaches such as mutational analyses elicited variable outcomes [12, 15–18]. Two other *BRIP1* polymorphisms (*C47G* and *G64A*) have received less attention, but availability of genotype data in the literature warranted inclusion of these in our analysis. The *G64A* polymorphism (rs2048718) might affect gene regulation [17, 19]; however, studies have demonstrated no associations of this polymorphism with breast cancer [19, 20]. On the other hand, the *C47G* polymorphism (rs4988351) has been demonstrated to have a study-specific increased risk effect for the *G* variant [21]. The increasing number of reports and discrepancy of the findings for the *BRIP1* polymorphisms in breast cancer prompted us to perform a meta-analysis.

Materials and methods

The literature search

We adopted four search strategies in MEDLINE using PubMed to look for association studies as of October 2012. In all four, we used "*breast cancer*" in combination with each of the following terms: "*BRIP1*" "*BACH1*", "*FANCJ*" and "*Fanconi anemia.*" The resulting four combinations or strategies yielded 79, 54, 42, and 215 citations, respectively. The last three strategies culminated in the same identity of articles as the first one ("*BRIP1*" and "*breast cancer*"), which we thus opted to use, outlined in Fig. 1. Of the 79 citations, 16 were retrieved as full text for further evaluation. Studies were eligible if they had genotypic data with a case–control design. Eight studies [10–12, 16–19, 21] were eventually included in this meta-analysis, which focused on the *Pro919Ser* polymorphism. Of the eight, two other polymorphisms (*C47G* and *G64A*) were included in three [16, 17, 21] and two [16, 19] studies, respectively (Table 1).

Data extraction and power calculations

Two investigators independently extracted data and reached consensus on all the items. The following information was obtained from each publication: first author's name, published year, country of origin, dominant ancestry of the study populations, matching criteria, sample source, genotype data, number of cases and controls. We also calculated frequencies of the variant allele, deviations of controls from the Hardy–Weinberg equilibrium (HWE) as well as statistical power of each study. Assuming odds ratio (OR) of 1.5 at a genotypic risk level of $\alpha = 0.05$ (two-sided), power was considered adequate at $\geq$80 %.

Meta-analysis

Risks (ORs) of breast cancer with the *Pro919Ser BRIP1* polymorphisms were estimated for each study. Frequency of the *Ser* allele is minor in six of the eight studies but not in Vahteristo et al. [12] and Frank et al. [19]. Given non-uniformity of the minor allele frequency across the studies, we thus compared the following for *Pro919Ser*: (i) *Ser* allele with *Ser-Pro/Pro-Pro* genotype, (ii) *Pro* allele with

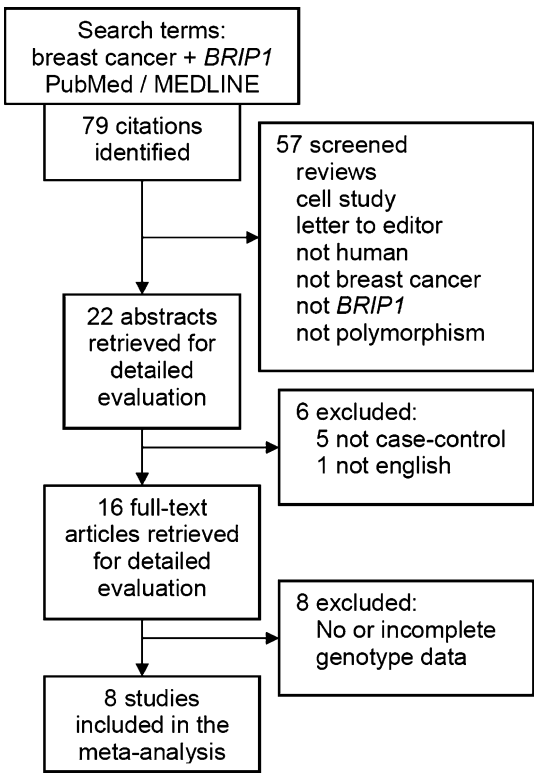

Fig. 1 Summary flowchart of the literature search

Table 1 Characteristics of the included studies associating *BRIP1* polymorphisms in breast cancer

First author (year)	Country	Ancestry of subjects	*BRIP1* polymorphisms						State of controls	Matching	Sample source	Power[a] ($\alpha = 0.05$, OR = 1.5)	vaf in controls	HWE
			Pro919Ser		*C47G*		*G64A*							
			Cases	Controls	Cases	Controls	Cases	Controls						
Rutter (2003) [17]	USA	European	116	60	116	58	–	–	Cancer-free	Ethnic	No mention	24.0	0.40	0.83
Closas [21] (2006)	USA	European	1,596	1,254	1,327	1,056	–	–	No mention	Age ±5	Buccal	99.9	0.43	0.84
Guenard (2008) [16]	Canada	French Canadian	96	70	96	69	96	70	Healthy	No mention	Blood	24.4	0.60	0.69
Seal (2006) [10]	UK	White, non-UK ethnic groups were excluded	1,212	2,081	–	–	–	–	No mention	Age	Blood	99.9	0.39	0.34
Vahteristo (2006) [12]	Finland	European	866	731	–	–	–	–	Healthy	Geography	Blood	97.8	0.54	0.17
Frank (2007) [19]	Germany	European	571	712	–	–	571	712	Healthy	Ethnic	Blood	94.4	0.43	0.20
Silvestri (2011) [18]	Italy	European	97	203	–	–	–	–	Healthy	Geography	Blood	36.5	0.36	0.85
Huo (2009) [11]	China	Han	568	624	–	–	–	–	Cancer-free	Age, residence	No mention	93.1	0.26	0.36

vaf variant allele frequency, *HWE* Hardy–Weinberg equilibrium

[a] Based on the number of cases and controls in the *Pro919Ser* polymorphism

Table 2 Summary effects of *BRIP1 Ser919Pro* polymorphism in breast cancer

	N (cases/controls)	Pro allele				Ser allele				Pro-Ser genotype			
		OR (95 % CI)	*P*	P_{het}	I^2	OR (95 % CI)	*P*	P_{het}	I^2	OR (95 % CI)	*P*	P_{het}	I^2
Overall	8 (5,122/5,735)	1.02 (0.94–1.11)	0.62	0.98	0	1.01 (0.91–1.12)	0.83	0.75	0	0.98 (0.90–1.05)	0.53	0.84	0
European only	6 (4,458/5,041)	1.03 (0.94–1.12)	0.52	0.95	0	1.03 (0.93–1.15)	0.53	0.87	0	0.96 (0.88–1.04)	0.27	0.92	0
Power													
>80 %	5 (4,813/5,402)	1.02 (0.94–1.11)	0.67	0.96	0	1.03 (0.93–1.14)	0.60	0.69	0	0.97 (0.89–1.05)	0.43	0.64	0
Menopausal status													
Pre-	2 (682/843)	0.94 (0.74–1.19)	0.60	0.63	0	0.98 (0.77–1.25)	0.87	0.40	0	**1.39 (1.13–1.71)**	**0.002**	**0.11**	**60**
Post-	2 (755/600)	1.16 (0.89–1.51)	0.28	0.59	0	1.12 (0.85–1.47)	0.42	0.90	0	0.83 (0.66–1.04)	0.11	0.55	0

All comparisons used the fixed-effects model

Significant increased risk effects ($P \leq 0.05$) are in bold

N number of studies, *OR* odds ratio, *CI* confidence interval, P_{het} *P* value for heterogeneity

Ser-Pro/Pro-Pro genotype, and (iii) *Pro/Ser* genotype with homozygous *Pro-Pro* and *Ser-Ser* genotypes.

Given uniformity of the minor allele frequencies for *G64A* and *C47G* in the included studies, pooled ORs were calculated following the standard genetic models: (i) additive: (*AA* and *GG* genotypes compared with the *GG* and *CC*, respectively in *G64A* and *C47G*), (ii) allelic: (frequency of variant alleles [*A* and *G*] assuming the risk could differ across all three genotypes), (iii) recessive (*AA* vs. *AG* + *GG; CC* vs. *CG* + *GG*) and (iv) dominant: (*AA* + *AG* vs. *GG; CC* + *CG* vs. *GG*).

To compare effects on the same baseline, we used raw data to calculate pooled ORs which were obtained using either the fixed [22] (in the absence of heterogeneity) or random [23] (in its presence) effects models. Heterogeneity between studies was estimated using the χ^2-based Q test [24]. Given the low power of this test [25], significance threshold was set at $P = 0.10$. Heterogeneity between studies was estimated using the χ^2-based Q test [24], explored using subgroup analysis [24] with menopausal status as variables, and quantified with the I^2 statistic which measures degree of inconsistency among studies [26]. Data were analyzed using Review Manager 4.3 and SigmaStat 2.03. Significance was set at a *P* value of $\leq$0.05 throughout except in heterogeneity estimation. Publication bias was not investigated because of the low sensitivity of the qualitative and quantitative tests when the number of studies is lower than ten [27].

Results

Overall

We undertook a meta-analysis using data from eight studies (5,122 cases/5,735 controls) where we investigated association of three *BRIP1* polymorphisms with breast cancer risk. Table 2 shows the *Pro919Ser* findings where null effects (OR 0.98–1.02) were detected in the overall analysis. Confined to the majority of samples represented by European originated Caucasians (six studies: 4,458 cases/5,041 controls), the null effects remained (OR 0.96–1.03). Confining the studies with >80 % statistical power (five studies: 4,813 cases/5,402 controls) also showed null associations (ORs 0.97–1.03). Consistent with the *Pro919Ser* findings, *G64A* effects, from two studies (667 cases/782 controls) were also null (OR 0.90–0.98) as shown in Table 3. Tables 2 and 3 show that all these findings were observed in the absence of heterogeneity ($I^2 = 0$ %) indicating that the studies are similar enough to be pooled. Only the *C47G* polymorphism, from three studies (1,539 cases/1,183 controls) differed in pooled effects where non-significant increased risks for the *Pro-Ser* genotype were observed (OR 1.27–1.40, $P = 0.12$–0.26) under variable heterogeneous conditions ($I^2 = 25$–74 %) (Table 3).

Subgroup analysis

Table 2 shows the stratified analysis by age (below and above 50) which corresponds to premenopausal (<50 years) and postmenopausal (≥50 years) status [12]. Results in the premenopausal group (682 cases/843 controls) were essentially null for the *Pro* (OR 0.94) and *Ser* alleles (OR 0.98). *Pro-Ser* genotype associations in this group of women, however, indicated significant increased risk (OR 1.39, $P = 0.002$). Pooled ORs among postmenopausal women (755 cases/600 controls) spanned a range of non-significantly protective effects (OR 0.83, $P = 0.11$) for the *Pro-Ser* genotype to slightly increased risk (OR 1.12–1.16, $P = 0.28$–0.42) for the *Ser* and *Pro* alleles. Except for premenopausal *Pro-Ser* genotype ($I^2 = 60$ %), all were obtained in the absence of heterogeneity ($I^2 = 0$ %).

Table 3 Summary effects of *BRIP1 C47G* and *G64A* polymorphisms in breast cancer

	BRIP1 polymorphism, number of studies (cases/controls)							
	C47G, 3 (1,539/1,183)				*G64A*, 2 (667/792)			
	OR (95 % CI)	P	P_{het}	I^2	OR (95 % CI)	P	P_{het}	I^2
Homozygous	1.30 (0.94–1.79)	0.12	0.25	27	0.90 (0.67–1.22)	0.50	0.51	0
Recessive	1.27 (0.92–1.74)	0.15	0.41	0	0.90 (0.69–1.16)	0.41	0.74	0
Dominant	1.33 (0.81–2.19)	0.26	**0.04**^{R}	68	0.98 (0.78–1.22)	0.85	0.38	0
Allele	1.40 (0.89–2.21)	0.14	**0.02**^{R}	74	0.96 (0.82–1.11)	0.56	0.42	0

Significant increased risk effects ($P \leq 0.05$) are in bold

OR odds ratio, *CI* confidence interval, *R* random-effects model

Assessment of study quality

We examined association of three *BRIP1* polymorphisms (*Pro919Ser*, *G64A*, and *C47G*) with breast cancer risk from a population with a European dominated ancestry indicating minimal admixture. Table 1 summarizes features of the included studies. In all three polymorphisms, the eight studies had control frequencies that conformed to the HWE. Of the eight studies, five [10–12, 19, 21] had a total sample size >1,000 which corresponded to high statistical power (93–99.9 %). Controls were either healthy or cancer-free in six (75 %) studies [11, 12, 16–19]. Six studies (75 %) mentioned tissue source samples, and of the six, five (83 %) used blood as source material [10, 12, 16, 18, 19]. Controls for seven studies (88 %) were matched on levels of age, ethnicity, and geography. Of the seven, three (43 %) used the age criterion [10, 11, 21] and two studies each (29 %) used ethnicity [17, 19] as well as geography [12, 18].

Discussion

With a sample size of over 10,800, our meta-analysis has shown overall null association between the *Pro* and *Ser* alleles as well as *Pro-Ser* genotype and breast cancer. This effect was materially unaltered even when confined to subjects of European ancestry, which comprise the majority (75 %) of our study populations. Allowing a Type I error of 5 %, the present meta-analysis has power greater than 80 % to detect an effect size of 1.5 for the overall and European analyses. Confined to high (>80 %) statistical power, the *BRIP1 Pro919Ser* findings were still null, all without evidence of heterogeneity. These null findings agree with two studies [12, 14] which found no evidence of association between *Pro919Ser* and breast cancer risk.

Subgrouped by age and thus menopausal status, the *Pro919Ser* polymorphism outcomes were still null for the *Pro* and *Ser* alleles in the premenopausal (<50 years) studies, without evidence of heterogeneity. However, our *Pro-Ser* genotype analysis yielded significant 1.4-fold increased risk effects which concur with another study that found a 7-fold increased risk among women to the age 50 from a kin-cohort population [13]. In that study, the relative cumulative risk by the age 50 years was 6.9 for *Ser* homozygotes ($P = 0.02$). When extended to age 70 years, no significant association was seen (OR 1.3, $P = 22$) which was similar to our postmenopausal findings of non-significant 1.2-fold increased risk. Although our meta-analysis data suggest that *Pro919Ser* polymorphism is not a breast cancer predisposition allele, a low risk effects cannot be discounted. Joint effect of the *Pro919Ser* variant as well as other epidemiological risk factors such as genetic background and environmental influence may be possible.

Null findings of the *G64A* polymorphism concur with two other studies that observed no associations with breast cancer [13, 14]. On the other hand, *C47G* had up to 1.4-fold increased risk in the dominant and allelic models with evidence of heterogeneity. Heterogeneity was not evident in the homozygous and recessive models where susceptibility effects were 1.3-fold. In these models, however, the Garcia-Closas et al. [21] study accounted for 91 % weight contribution to the summary effects (data not shown). This indicates that the summary effects of *C47G* polymorphism is attributed towards this one study. More studies required to achieve more robust conclusions especially confirm the increased risk outcomes in *C47G* and null results of *G64A*.

The strength of our meta-analysis includes: (i) large sample sizes in the overall and European analyses, (ii) ethnic homogeneity in three-fourth of the studies, (iii) controls were healthy, (iv) a high proportion (88 %) of the studies were matched to cases; (v) majority (63 %) of the component studies had high statistical power and (vi) consistent no significant associations in the allele/genotype comparisons and across all genetic models under conditions of consistent zero heterogeneity, rendering chance effects less likely. All these features indicate unlikelihood of selection bias as well as non-differential misclassification bias because the issue of different risks in the control groups of developing breast cancer has been modulated.

Conclusion

To our knowledge, this is the first meta-analysis approach that investigates into associations of three *BRIP1* polymorphisms with breast cancer risk. Our results demonstrate that variant alleles in two (*Pro919Ser* and *G64A*) of the three *BRIP1* polymorphisms elicited no associations with breast cancer risk, confirmed in the subgroup analysis for *Pro919Ser*. Thus, both polymorphisms are not independent risk factors for breast carcinogenesis. Such analysis may shed light on the complexities in the *BRCA* pathway providing hypotheses for future functional studies. Increased risk effects of the *C47G* polymorphism are beset with heterogeneity, although consistent for its increased risk effects in all genetic models. However, these results require more studies for confirmation.

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Conflict of interest The authors declare that they have no conflict of interest.

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