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EPIDEMIOLOGY

Association between polymorphisms of the ataxia telangiectasia mutated gene and breast cancer risk: evidence from the current studies

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Abstract Epidemiological studies have evaluated the association between ataxia telangiectasia mutated (ATM) gene polymorphisms and breast cancer risk. However, published data are still inconclusive. We performed a meta-analysis for the first time, based on currently available evidence, by searching PubMed, ISI Web of Knowledge, and Embase databases to derive a more precise assessment of the relationship. Following the inclusion and exclusion criteria, nine publications were included in this meta-analysis. Of these studies, one had a deviation from the Hardy–Weinberg equilibrium (HWE) at a statistical significance level of 0.01 in controls, and another two had no available data for HWE. We observed that the ATM 5557G>A polymorphism was significantly correlated with breast cancer risk when all studies were pooled into the meta-analysis (recessive model: odds ratio, OR = 0.67; 95% confidence interval (CI) 0.51–0.89). For the ATM IVS38-8T>C polymorphism, no significant association was found in the allele contrast, heterozygote codominant, and dominant models. There were no available data to perform this meta-analysis in the homozygote codominant and recessive models. For the ATM IVS1+19A>T polymorphism, a significant association with breast cancer risk was found in the allele contrast model (C vs. T: OR = 1.60; 95% CI 1.02–2.52). For the IVS34+60G>A polymorphism, no significant association was found in the allele contrast, codominant, dominant, and recessive models. Egger's test did not suggest any evidence of publication bias ($P = 0.47$ for the recessive model). In conclusion, there is limited evidence to indicate that ATM polymorphisms are associated with increased risk of breast cancer.

Keywords Ataxia telangiectasia · Breast cancer · Genetic polymorphisms · Mutation · Risk

Pei-Hua Lu, Mu-Xin Wei and Min-bin Chen contributed equally to this study and should be considered as co-first authors.

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Introduction

The etiology of breast cancer is poorly understood. It is plausible that low-penetrance susceptibility genes combining with environmental factors may contribute to the pathogenesis and progression of breast cancer [1]. Common variants within genes involving breast carcinogenesis-related pathways are candidate loci for cancer susceptibility [2]. Mutations in the BRCA1 and BRCA2 genes (BRCA1/2) have been identified as high penetrance alleles. However, these alleles are associated with only a small fraction of breast cancers [3].

The ataxia telangiectasia mutated (ATM) gene has been frequently associated with hereditary breast cancer as a low-penetrance susceptibility gene[4]. ATM kinase has an essential role in maintaining genomic integrity. It is a key activator of the cellular responses to DNA double-strand breaks [5]. Heterozygous females with germline ATM mutations have been reported to have an increased risk of breast cancer. A number of studies have searched for germline ATM mutations in breast cancer cases and compared the frequency of common ATM variants among breast cancer cases to population controls, but evidence regarding the role of the ATM as a breast cancer susceptibility gene has been contradictory [6, 7].

Recently, large epidemiological and molecular studies have finally provided conclusive evidence that ATM polymorphisms that cause ataxia telangiectasia are also associated with breast cancer susceptibility [6, 8]. There was no evidence that other classes of ATM variants conferred a risk of breast cancer [8]. A common ATM variant IVS38-8T>C in cis with the 5557G>A ATM variant, has been suggested to be associated with breast cancer [9]. Heikkinen et al. [9], in their mutation analysis of the ATM gene in patients from 121 Northern Finnish breast or breast-ovarian cancer families, reported that the haplotype composed of the alleles 5557G>A and IVS38-8T>C was significantly associated with bilateral breast cancer. In a later report, Langholz et al. [10] in the WECARE Study population did not find that the haplotype of 5557G>A and IVS38-8T>C conferred an increased risk in women with bilateral breast cancer when compared with women with unilateral breast cancer. Inconclusive results were also found regarding the genotypes of IVS1+19A>T and IVS34+60G>A between breast cancer patients and controls [11–14]. Hence, the clinical relevance of this polymorphic gene remains unknown. In order to help resolve this ongoing uncertainty, we have performed a meta-analysis to further determine the association between ATM polymorphisms and risk of breast cancer.

Materials and methods

Search strategy

A comprehensive search was conducted to identify all case–control studies up to July 2010, using search strategy "ataxia-telangiectasia mutated," "ATM," "breast cancer," as well as "polymorphism" in PubMed, ISI Web of Knowledge, and Embase databases. All potentially eligible studies were retrieved, and their bibliographies were carefully evaluated to identify other eligible studies. Additional studies were identified by a hand search of the references of original studies. Only those studies published in the English language were included. When multiple studies of the same patient population were identified, we included the published report with the largest sample size.

Inclusion and exclusion criteria

The inclusion criteria were: (1) independent case–control or cohort studies that quantitatively assessed the relationship between the ATM 5557G>A, IVS 38-8T>C, IVS 1+19A>T, and IVS 34+60G>A polymorphisms and risk of breast cancer; (2) sufficient available data to estimate an OR with 95% CI; and (3) cases with breast cancer regardless of tumor stage or histological type. Major exclusion criteria were: (1) no control population, (2) no available genotype frequency, and (3) duplication of a previous study.

Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors (Lu and Chen) according to the inclusion criteria listed above. The following data were collected from each study: the first author's surname, publication year, country of origin, population ethnicity, characteristics of controls, genotyping method, numbers of genotyped cases and controls (GG, GA, and AA genotypes for the ATM 5557G>A polymorphism, TT, TC, and CC genotypes for the IVS 38-8T>C polymorphism, AA, A,T and TT genotypes for the ATM IVS 1+19A>T polymorphism, and GG, GA, and AA genotypes for the ATM IVS 34+60G>A polymorphism). Any disagreement was resolved by discussion until a consensus was reached between the two authors. If they could not reach a consensus, another author (Wei) was consulted to resolve the dispute, and a final decision was made by a majority of the authors. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical methods

The strength of association between ATM polymorphisms and breast cancer risk was measured by ORs with 95% CIs. We estimated the association under five different types of ORs, namely, the allele contrast model (A vs. G, C vs. T, T vs. A, or A vs. G), the homozygote codominant model (AA vs. GG, CC vs. TT, TT vs. AA, or AA vs. GG), the heterozygote codominant model (GA vs. GG, TC vs. TT, AT vs. AA, or GA vs. GG), the recessive model (AA vs. GG+GA, CC vs. TT+TC, TT vs. AA+AT, or AA vs. GG+GA), and the dominant model (AA+GA vs. GG, CC+TC vs. TT, TT+AT vs. AA, or AA+GA vs. GG for ATM polymorphisms). Hardy–Weinberg equilibrium (HWE) was tested by the Chi-square test. The Q-statistic was used to investigate the degree of heterogeneity between

the trials, and a P value > 0.10 for the Q-test indicated a lack of heterogeneity among studies. When there was no statistical heterogeneity, we used a fixed effects model (the Mantel–Haenszel method) [13]. If heterogeneity was present, we used a random effects model (DerSimonian–Laird method) to account for inter-study heterogeneity [14]. An estimate of publication bias was performed by visual inspection of a funnel plot, in which the standard error of log(OR) of each study was plotted against its log(OR). An asymmetric plot suggested a possible publication bias, and the degree of asymmetry was tested using Egger's test ($P < 0.05$ was considered to indicate significant publication bias). A sensitivity analysis was also performed by omitting each study in turn to identify potential outliers. All statistical tests were two-sided. The meta-analysis was performed using STATA version 10.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

In total, 49 studies were obtained by searching for articles on the relationship between ATM polymorphisms and breast cancer susceptibility. Following the above inclusion and exclusion criteria, nine publications were included in this meta-analysis [4, 11–18]. Some case–control studies presented the ORs separately for more than one kind of ATM polymorphism [4, 11, 15, 16]. Thus, a total of five studies were included in the meta-analysis with 2,604 cases and 1,973 controls for the ATM 5557G>A polymorphism, three studies with 1,972 cases and 1,220 controls for the ATM IVS38-8T>C polymorphism, three studies with 2,405 cases and 2,918 controls for the ATM IVS1+19A>T polymorphism, and two studies with 2,252 cases and 2,701 controls for the ATM IVS34+60G>A polymorphism. The characteristics of all the studies are summarized in Table 1. Of these studies, the sample sizes ranged from 184 [13] to 2,884 [11] individuals. One study deviated from the HWE at a significance level of $P = 0.01$ in controls [11] and another two studies by Mehdipour et al. [18] and Koren et al. [13] had no available data for HWE. The genotypes and separate P values for ATM 5557G>A, IVS38-8T>C, IVS1+19A>T, and IVS34+60G>A polymorphisms included in the meta-analysis are shown in Table 2. Almost all of the cases were pathologically confirmed. Controls were mainly healthy populations and matched for age.

Meta-analysis result

Table 3 lists the main results of pooled ORs for ATM polymorphisms and breast cancer risk. We observed that the ATM 5557G>A polymorphism was significantly correlated with breast cancer risk when all studies were pooled into the meta-analysis (recessive model: OR = 0.67, 95% CI 0.51–0.89, Fig. 1). For the ATM IVS38-8T>C polymorphism, no significant association was found in the allele contrast model (C vs. T allele contrast: (OR = 1.32, 95% CI 0.97–1.80, fixed effects model, Fig. 2), the heterozygote codominant model, and the dominant models. There were no available data for performing this meta-analysis in the homozygote codominant and recessive models. For the ATM IVS1+19A>T polymorphism, a significant association with breast cancer risk was found in the allele contrast model (C vs. T allele contrast: OR = 1.60, 95% CI 1.02–2.52, random effects model, Fig. 3). For the IVS34+60G>A polymorphism, no significant association was found in the allele contrast model (C vs. T allele contrast: OR = 1.02, 95% CI 0.94–1.11, fixed effects model, Fig. 4), nor in the codominant, dominant, and recessive models.

Sensitivity analysis

We checked the inclusion criteria of this meta-analysis by a sensitivity analysis. Pooled estimates for all genetic models were insensitive to the removal of individual studies, and the corresponding pooled ORs were not substantially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Publication bias was assessed by a visual inspection of the Begg's funnel plot (Fig. 5) of the ORs of the recessive model for ATM 5557G>A polymorphism. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (figure not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.47$ for the recessive model).

Discussion

Heterozygous females with germline ATM mutations have been reported to have an increased risk of breast cancer, but evidence regarding the role of ATM as a breast cancer susceptibility gene has been contradictory [6, 7]. A common ATM variant IVS38-8T>C in cis with the 5557G>A ATM variant, has been suggested to be associated with bilateral breast cancer [9]. The ATM gene 5557G>A polymorphism also was the ATM gene (p.D1853N) (rs1801516) polymorphism. Langhol et al. [10]

Table 1 Main characteristics of the studies with ATM 5557G>A, IVS38-8T>C, IVS1+19A>T, and IVS34+60G>A polymorphisms included in the meta-analysis

First author/published year	Study population of cases	Genotyping method	Source	Cases	Controls	HWE of controls
ATM 5557G>A						
Mehdipour [18] 2010	Iranian, Asian, patients affected with primary breast cancer. External and internal controls were 42.2 ± 11.7 and 36 ± 17 years old	PCR	HB	129	248	NA
Schrauder [17] 2008	Germany, Caucasians, unselected patients. Median age at onset of breast cancer was 55.8 ± 11.6 years	Real-time PCR	HB	514	511	0.668
Gonzalez-Hormazabal [4] 2008	Chile, Caucasians, familial breast cancer cases without BRCA1/2 mutations, Age range not stated	PCR-RFLP	PB	126	200	0.326
Tommiska [16] 2006	Finnish, Caucasians, unselected and familial breast cancer patients, Age range not stated	PCR-RFLP	PB	1581	702	0.648
Angele [15] 2003	France, Caucasians, breast cancer women received radiotherapy, Age range 35–81 years	RFLP + SOMA + Sequencing + DHPLC	HB	254	312	0.306
ATM IVS38-8T>C						
Gonzalez-Hormazabal [4] 2008	Chile, Caucasians, familial breast cancer cases without BRCA1/2 mutations, Age range not stated	PCR- RFLP	PB	126	200	0.829
Tommiska [16] 2006	Finnish, Caucasians, unselected and familial breast cancer patients, Age range not stated	PCR-RFLP	PB	1592	708	0.439
Angele [15] 2003	France, Caucasians, breast cancer women received radiotherapy, Age range 35–81 years	RFLP + SOMA + Sequencing + DHPLC	HB	254	312	0.621
ATM IVS1+19A>T						
Ye [14] 2007	Chinese women, Asians, recruited two sets of cases, between 20 and 70 years	PCR	PB	1065	1158	0.704
Koren [13] 2006	Israel, Asians, none of the study participants was a carrier of any of the predominant Jewish mutations in BRCA1/2, Mean age was 48.3 ± 9.7 years	PCR	PB	66	118	NA
Tamimi [11] 2004	USA, Caucasians. Cases were excluded if they had any other prior cancer diagnosis, age 30–55 years	PCR	Nested	1274	1642	0.032
ATM IVS34+60G>A						
Lee [12] 2005	Korean, Asian patients, exclusion of breast cancer patients with previous history of cancer or previous history of hysterectomy and oophorectomy, age range not stated	PCR	PB	982	1087	0.288
Tamimi [11] 2004	USA, Caucasians, cases were excluded if they had any other prior cancer diagnosis, age 30–55 years	PCR	Nested	1270	1614	0.092

NA not available, *ATM* ataxia telangiectasia mutated gene, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism, *SOMA* short oligonucleotide mass analysis, *DHPLC* denaturing high performance liquid chromatography, *HWE* Hardy–Weinberg equilibrium, *PB* population-based study, and *HB* hospital-based study

did not find that the haplotypes of 5557G>A and IVS38-8T>C conferred an increased risk to women with bilateral breast cancer in the WECARE Study. The IVS34+60 GA or AA genotypes were associated with increased breast cancer risk in Korea, particularly in premenopausal Korean women [12]. However, Tamimi et al. [11] failed to find an association between ATM IVS34+60 and breast cancer risk. Obscure results were also found in the genotypes of IVS1+19A>T between breast cancers and controls [11, 13, 14]. Hence, as conflicting results have been obtained, the clinical relevance of this polymorphic gene remains uncertain. Thus, we performed this meta-analysis of the association between the ATM polymorphisms and risk of breast cancer.

Table 2 Genotypes and *P* values of ATM 5557G>A, IVS38-8T>C, IVS1+19A>T, and IVS34+60G>A polymorphisms included in the meta-analysis

Author	Cases					Controls					*P* value, OR (95% CI)
5557G>A	GG	GA	AA	G	A	GG	GA	AA	G	A	
Mehdipour et al. [18]	40[a]		89	–	–	46[a]		202	–	–	0.005, 2.579 (1.337–4.975)
Schrauder et al. [17]	406	99	9	911	117	369	129	13	867	155	0.04, 0.70 (0.52–0.94)
Gonzalez-Hormazabal et al. [4]	100	26	0	226	26	174	26	0	374	26	0.048, 1.74 (0.96–3.16)
Tommiska et al. [16]	954	561	66	2469	693	404	260	38	1068	336	0.27, 0.89 (0.72–1.09)
Angele et al. [15]	192	56	6	440	68	240	65	7	545	79	NA, 1.08 (0.72–1.61)
Author	Cases					Controls					*P* value, OR (95% CI)
IVS38-8T>C	TT	TC	CC	T	C	TT	TC	CC	T	C	
Gonzalez-Hormazabal et al. [4]	115	11	0	241	11	194	6	0	394	6	0.024, 3.09 (1.11–8.59)
Tommiska et al. [16]	1486	106	0	3078	106	668	40	0	1376	40	0.083, 1.06 (0.69–1.64)
Angele et al. [15]	236	18	0	490	18	295	17	0	607	17	NA, 1.32 (0.68–2.63)
Author	Cases					Controls					*P* value, OR (95% CI)
IVS1+19A>T	AA	AT	TT	A	T	AA	AT	TT	A	T	
Ye et al. [14]	315	523	227	1153	977	340	569	249	1249	1067	0.97, 1.0 (1.0–1.3)
Koren et al. [13]	–	–	–	88	44	–	–	–	227	9	0.35, 0.08 (0.04–0.17)
Tamimi et al. [11]	450	575	249	1475	1073	556	762	324	1874	1410	0.63, 0.95 (0.77–1.17)
Author	Cases					Controls					*P* value, OR (95% CI)
IVS34+60G>A	GG	GA	AA	G	A	GG	GA	AA	G	A	
Lee et al. [12]	183	513	286	879	1085	248	524	315	1020	1154	<0.05, 1.29 (1.04–1.60)
Tamimi et al. [11]	455	570	245	1480	1060	553	755	306	1861	1367	0.51, 1.03 (0.83–1.28)

– No available data, *OR* odds ratio, and *CI* confidence interval

[a] GG + GA genotypes

Table 3 Main results of pooled ORs for ATM 5557G>A, IVS38-8T>C, IVS1+19A>T, and IVS34+60G>A polymorphisms

Study groups	Variables[a]	Allele contrast model		Homozygote codominant	
		OR(95% CI)	Ph	OR (95% CI)	Ph
5557G>A	5	0.94 (0.74–1.20)	0.041	0.74 (0.52–1.06)	0.754
IVS38-8T>C	3	1.32 (0.97–1.80)	0.238	–	–
IVS1+19A>T	3	1.60 (1.02–2.52)[b]	0.000	0.96 (0.83–1.13)	0.824
IVS34+60G>A	2	1.02 (0.94–1.11)	0.173	1.07 (0.91–1.26)	0.157

Study groups	Heterozygote codominant		Dominant model		Recessive model	
	OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph
5557G>A	0.96 (0.73–1.27)	0.041	0.95 (0.72–1.26)	0.033	0.67 (0.51–0.89)[b]	0.519
IVS38-8T>C	1.33 (0.97–1.82)	0.228	1.33 (0.97–1.82)	0.228	–	–
IVS1+19A>T	0.96 (0.84–1.09)	0.632	0.96 (0.85–1.08)	0.657	0.99 (0.86–1.13)	0.996
IVS34+60G>A	1.09 (0.76–1.57)	0.010	1.09 (0.79–1.49)	0.016	1.01 (0.89–1.16)	0.916

[a] Number of comparisons

[b] Statistically significant results

– no available data to perform meta-analysis, *Ph P* value of Q-test for heterogeneity test

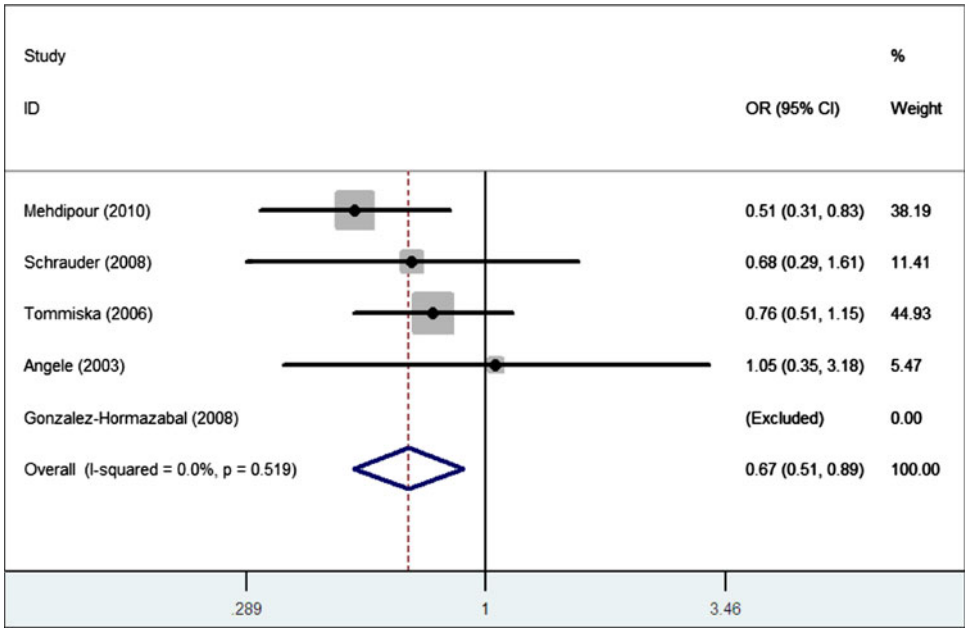

Fig. 1 Forest plot for the overall association between the ATM 5557G>A polymorphism and breast cancer risk (for the recessive model: AA vs. GA+GG). The study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for the OR (*horizontal lines*); the pooled OR and 95% CI have been appropriately derived from the fixed effects model

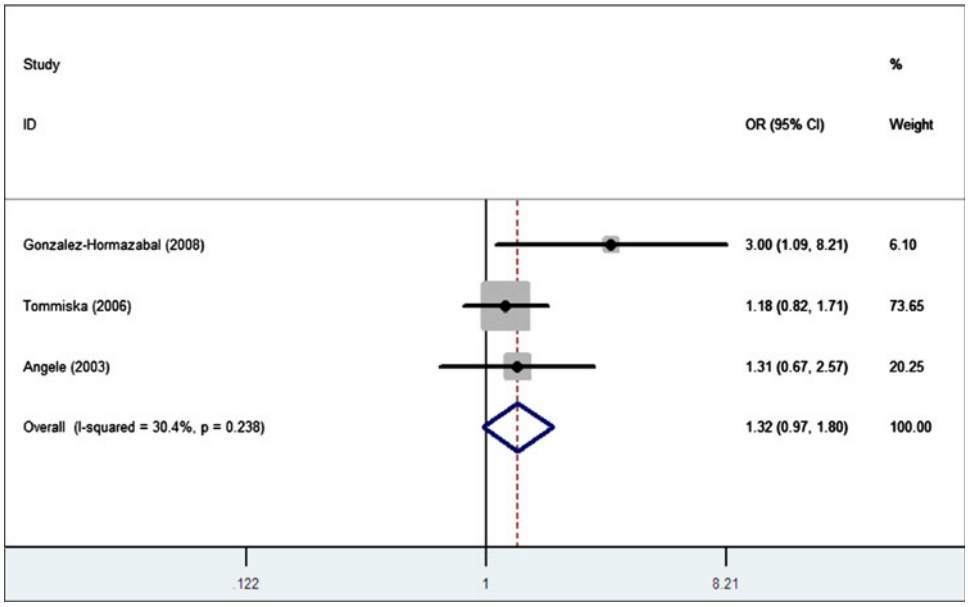

Fig. 2 Forest plot for the association between the ATM IVS38-8T>C polymorphism and breast cancer risk (for C vs. T allele contrast model, fixed effects model)

For the ATM 5557G>A polymorphism, a significant association with breast cancer risk was found when all studies were pooled into the meta-analysis (recessive model: OR = 0.67, 95% CI 0.51–0.89). For ATM IVS38-8T>C and IVS34+60G>A polymorphisms, no significant associations were found in the allele contrast, codominant, the dominant models, nor in the recessive models. For the IVS1+19A>T polymorphism, we observed that it was significantly correlated with breast cancer risk (C vs. T allele contrast model: OR = 1.60, 95% CI 1.02–2.52). Heterogeneity is a potential problem that may affect the interpretation of the results. There was statistically significant heterogeneity in the overall comparisons, but the results obtained using the random effects model were consistent with those from the fixed effects model.

Considering some limitations of this meta-analysis, our results should be interpreted with caution. First, the controls were not uniformly defined. Although most of the controls were selected mainly from predominantly healthy populations, some may have had benign disease. Therefore, non-differential misclassification bias is possible, as the control populations may have had different risks of developing breast cancer. Second, some of the subgroup analyses may have had insufficient statistical power to detect an association. We were also unable to examine gene-environment interactions which may be an important

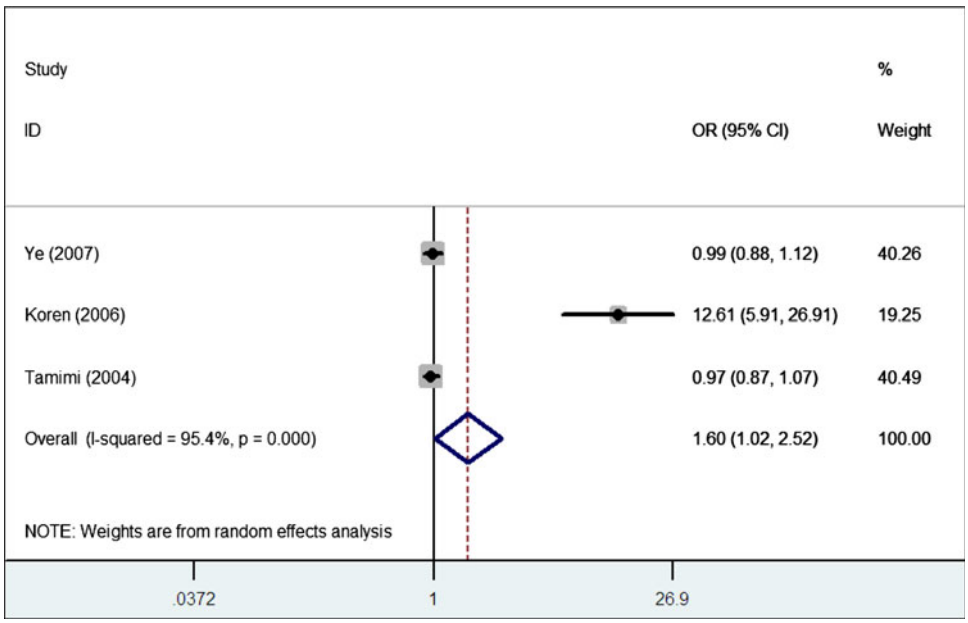

Fig. 3 Forest plot for the association between the ATM IVS1+19A>T polymorphism and breast cancer risk (for T vs. A allele contrast model, random effects model)

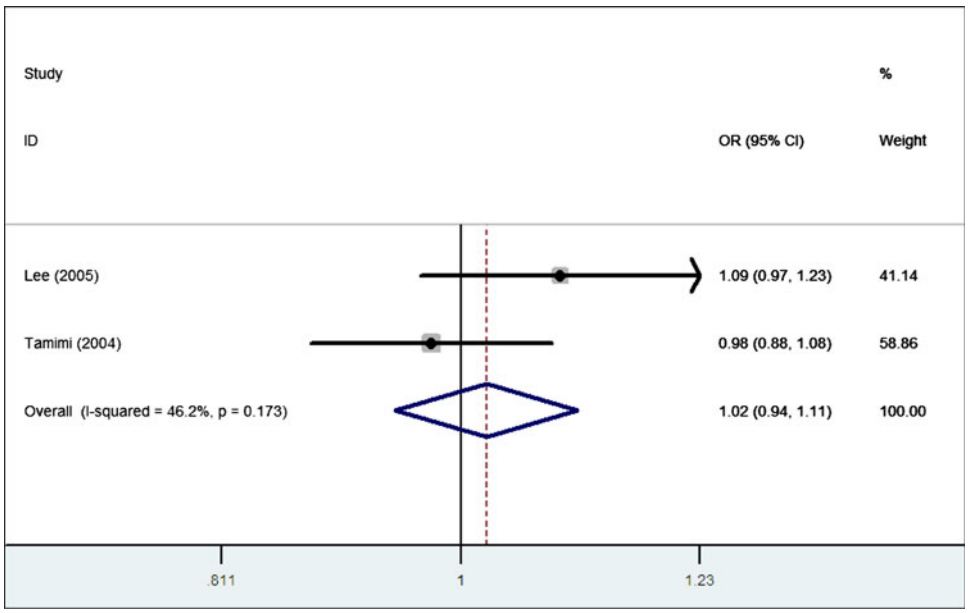

Fig. 4 Forest plot for the association between the ATM IVS34+60G>A polymorphism and breast cancer risk (for the A vs. G allele contrast model, fixed effects model)

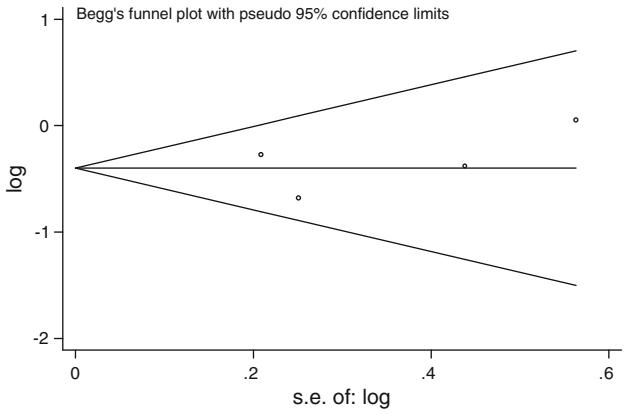

Fig. 5 Funnel plot analysis of the ORs of the recessive model for the ATM 5557G>A polymorphism

component of the association between the ATM 5557G>A, IVS 38-8T>C, IVS 1+19A>T, and IVS 34+60G>A polymorphisms and risk of breast cancer. Third, our results were based on unadjusted published estimates, and hence, we were unable to adjust them by possible confounders such as age, ethnicity, smoking, menopausal status, obesity, alcohol consumption, and other lifestyle risk factors.

In conclusion, the results of this meta-analysis indicate an overall lack of association between ATM polymorphisms and risk of breast cancer. However, there was some suggestion that the ATM 5557G>A and IVS1+19A>T polymorphisms were weakly associated with an increased risk of breast cancer, but this warrants further investigation in large, well-designed studies.

Conflict of interest None.

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