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An Association of Caspase-10 (Ex 1228G>A) Polymorphism with Breast Cancer Risk: A Meta-Analysis of Case-Control Studies

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Abstract

Background: Breast Cancer (BC) is one of the primary causes of cancer related deaths in women worldwide. The incidence rate of BC has increased in recent times, especially in developing countries. Several polymorphisms have been linked with susceptibility of breast cancer risk. Cellular differentiation and homeostasis is maintained by a coordinated cascade of apoptotic genes, caspases and any alternation in this pathway can potentially lead to cancer. Transition mutation in the 9th exon of caspase-10 is associated with breast cancer susceptibility with few reservations. We performed meta-analysis to examine the association of caspase-10 on exon 9 1228G>A polymorphism with BC susceptibility.

Method: Three studies with a total of 31,300 BC cases and 34,331 healthy controls were included in the analysis. The present analysis was performed using comprehensive meta-analysis Version 3 (CMA Version 3) software. Either random or fixed models were used according to the degree of heterogeneity within the studies. Odds ratio with 95% CI was calculated and was considered to apprise the association of caspase-10 on exon 9 1228G>A polymorphism with BC susceptibility with breast cancer risk.

Results and Discussion: The present meta-analysis showed that caspase-10, exon 9 1228G>A polymorphism was not associated with cancer risk (OR=0.91, 95%CI=0.77-1.08, p=0.30). Homozygous mutant AA analysis also did not show any significant association with BC (OR=0.93, 95%CI=0.73-1.18, p=0.58). All the case-control studies included in the analysis were Caucasian origin, therefore a larger case-control studies in different ethnic groups is inevitable to better understand the association of caspase-10 1228G>A polymorphism with BC risk.

Conclusion: The current meta-analysis result suggests that caspase-10, exon 9 1228G>A polymorphism is not associated with breast cancer risk.

Keywords: Breast cancer; Caspase-10; Polymorphism; Meta-analysis

Introduction

During the transformation of normal cell into cancerous cell the accumulation of genetic mutations occur which leads to loss of cellular functions [1]. Also, the normal cells undergo a series of phenotypic changes (hyperplasia, *in situ* carcinoma and invasive carcinoma) [2]. Apoptosis, the programmed cell death eliminates the abnormal cells developed during cellular pathology and excess cells during developmental stages. In cancer, however, the abnormal cells evade apoptosis either by mutation or by aberration in the apoptotic response [3,4]. Apoptosis is regulated by a cascade of cysteine aspartyl proteases that cleaves and eliminates the unwanted intracellular substrates from the cellular system. Caspases are of two types, initiator caspases (caspase 2, 8, 9, 10) and executioner caspases (caspase 3, 6, 7) [5].

Deregulation of apoptosis is one of the hallmarks of cancer including breast cancer [6] and several other diseases [7]. Apoptosis can be evaded by inhibition of either caspase functions or signal for initiation [8]. Caspase-10, out of several caspases discovered is an initiator caspase and its mutation has been detected in several cancers [9-12]. The functional role of caspase-10 point mutation at exon 9, nucleotide position 1228 from Guanine (G) to Adenine (A) (or from amino acid valine (V) to Isoleucine (I)) is not yet known. *In-vivo* study of this mutation is not yet analysed, but *in-vitro* transfection of the cDNA carrying mutation G to A showed attenuated apoptotic function in HEK293 cells [9]. It has been hypothesized that procaspase-10 is cleaved at D415 located between large and small subunits. More importantly the V410I mutation is located five amino acids upstream of the cleavage site and seven amino acids downstream of active-site motif [10].

Therefore, the amino acid change from valine to isoleucine at position 410 of caspase-10 might be important for impaired caspase activation. Frank et al. also suggested that caspase-10 variation might be one the causative reason for familial breast cancer [10]. However, Gaudet and Engel et al. demonstrated the presence of caspase-10 mutation was rare in BC [11,12]. Thus, to address these inconsistencies we performed a systematic meta-analysis from the published case-control studies in BC.

Materials and Methods

Literature search and study eligibility

An extensive search was done in Pubmed, Google scholar, Science-direct and cross-references were checked using keywords "caspase-10 and polymorphism", "caspase-10 polymorphism", "rs13010627" or "caspase-10 V410I" or "caspase-10 1228G>A" and "breast cancer". The articles that contained only available genotype frequencies, case-control studies, written in English and BC risk studies were included in the analysis. Those studies which included overlapping data, no case-control study for caspase-10 polymorphism and not associated with cancer risk were excluded from the study. Three studies with a total of 31,300 BC cases and 34,331 healthy controls were analysed.

Data extraction

The published data were independently collected by two investigators (SC and BMK) to extract the following information: first author, year of publication, country, ethnicity, number of case and controls, genotype and allele frequencies for each case-control study. The disagreement between the authors was resolved after group discussion amongst the investigators and final decision was taken by SKM.

Statistical analysis

The statistical analysis was performed using the comprehensive meta-analysis (CMA) V3 software (Biostat, USA). The CMA V3 has advantage over other software's for computing meta-analysis [13,14]. The odd ratio (OR) and confidence interval (CI) was measured to check the strength of the association of caspase-10 1228G>A with breast cancer. The heterogeneity and variation between the studies were estimated using I2-based Cochran's Q statistic test. The inter-study variability that can attribute to heterogeneity can be represented by I2 value which ranges between 0 to 100%. The I2 values 0-25, 25-50, 50-75, 75-100% represent no, moderate, large and extreme heterogeneity [15]. When a significant p value ($p<0.01$) or I2 >50% indicated heterogeneity among the studies, the random effect model was used, or the fixed model was used [16,17]. The publication bias was checked by Begger funnel plot which was further re-evaluated using Egger's regression analysis, the p value of regression analysis less than 0.01 was considered to be significant. The sensitivity analysis was performed by sequential removal of the individual studies.

Results

Characteristics of the studies

According to the inclusion criteria, three studies were included for the analysis [10-12]. The characteristics of the study are represented in Table 1. All the studies included in the analysis were of Caucasian origin. A total of 31,300 BC cases and 34,331 healthy controls were examined for the association of caspase-10 1228G>A polymorphism with breast cancer susceptibility.

Genotype distribution												
Study (ref)	Year	Country	Ethnicity	Cancer type	Case			Control			Confirming method	P value HWE
					GG	GA	AA	GG	GA	AA		
Engel	2010	Multicenter	European	BC	3368	486	18	2903	433	19	RFLP-PCR	NA
Gaudet	2009	Multicenter	European	BC	23456	3352	109	26597	3706	126	Taqman/Sequenom iPLEX	NA
Frank	2006	Germany	European	BC	455	55	1	456	85	6	TaqMan/ Sequencing	0.0076

Table 1: Caspase-10 1228G>A polymorphism characteristics of studies included in meta-analysis.

Publication bias

Begger's funnel plot and Egger's regression analysis was performed to check the publication bias. Egger's regression analysis was used to measure asymmetry of the funnel plot. The funnel plots were symmetrical and also the Egger's linear regression analysis showed no statistical significance for publication bias ($p>0.05$). The funnel plots are depicted in Figures 1a-1e.

Begger's funnel plot of publication bias has been categorised and plotted as Overall A vs G, Homozygous mutant AA vs GG, Heterozygous mutant GA vs GG, Dominant Genetic model AA+GA vs GG, Recessive Genetic model AA vs GG+GA. Publication bias was assessed in studies assaying odds ratio of cancer associated with CASP10 1228G>A polymorphism. Begger's funnel plot showed no publication bias within the studies.

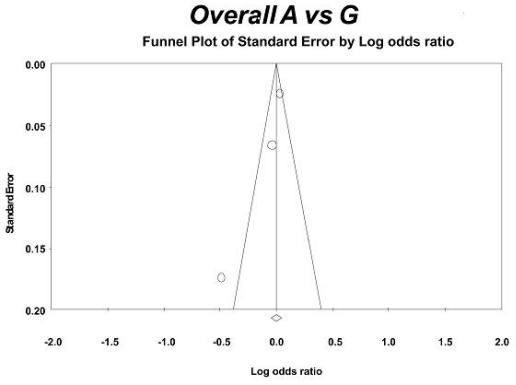

Figure 1(a): Begger's funnel plot of publication bias: Overall A vs G.

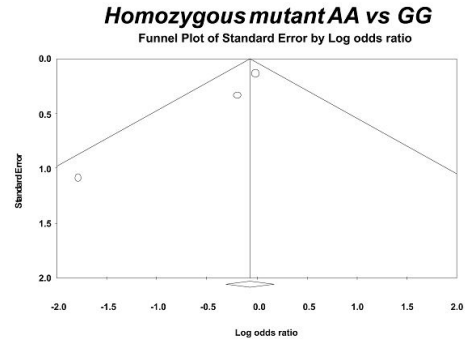

Figure 1(b): Begger's funnel plot of publication bias: Homozygous mutant AA vs GG.

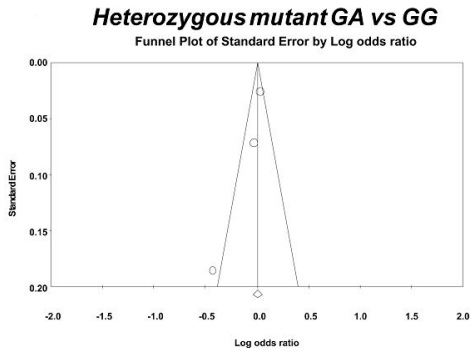

Figure 1(c): Begger's funnel plot of publication bias: Heterozygous mutant GA vs GG.

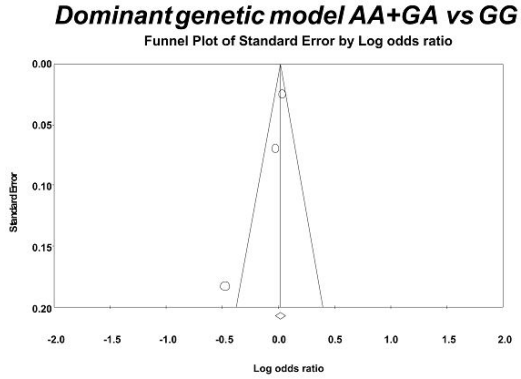

Figure 1(d): Begger's funnel plot of publication bias: Dominant Genetic model AA+GA vs GG.

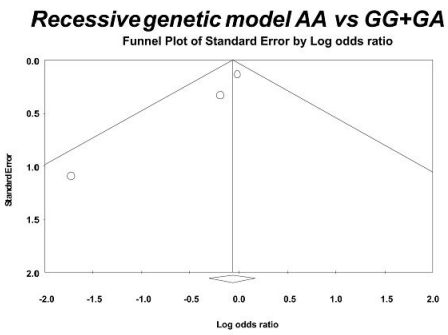

Figure 1(e): Begger's funnel plot of publication bias: Recessive Genetic model AA vs GG+GA.

Heterogeneity test

The heterogeneity among the studies was check by using Q-test and I2 statistics. The overall allele (A vs. G), heterozygous mutant (GA vs. GG) and dominant genotype model (AA+GA vs. GG) showed heterogeneity, therefore the random model was used (A vs. G: Q=9.48, Ph=0.009, I2=78.90; GA vs. GG: Q=6.44, Ph=0.04, I2=68.97; AA+GA vs. GG: Q=8.13, Ph=0.01, I2=75.40). Since homozygous mutant (AA vs. GG) and recessive genotype model (AA vs. GG+GA) showed no heterogeneity the fixed model was used (AA vs. GG: Q=2.83, Ph=0.24, I2=29.46; AA vs. GG+GA: Q=2.64, Ph=0.26, I2=24.39). All details are mentioned in Table 2.

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for meta-analysis
	Intercept	95% Confidence Interval	P value	Q value	Phetero geneity	I2 (%)	
A vs. G	-2.85	-24.41	0.1	9.481	0.009	78.9	Random
AA vs. GG	-1.59	-11.28	0.08	2.835	0.24	29.463	Fixed
GA vs. GG	-2.35	-19.73	0.1	6.44	0.04	68.97	Random
AA+GA vs. GG	-2.64	-22.43	0.1	8.13	0.01	75.4	Random
AA vs. GG + GA	-1.54	-10.96	0.08	2.64	0.26	24.39	Fixed

Table 2: Statistics to test publication bias and heterogeneity.

Meta-analysis results

The meta-analysis did not show any association between caspase-10 1228G>A polymorphism with BC. The overall variant allele A was not associated with BC (OR=0.91, 95%CI=0.77-1.08, p=0.30). In addition, heterozygous mutant AG (OR=0.94, 95%CI=0.81-1.09, p=0.46), homozygous mutant AA (OR=0.93, 95%CI=0.73-1.18, p=0.58), dominant (OR=0.92, 95%CI=0.78-1.09, p=0.36) and recessive models

(OR=0.93, 95%CI=0.73-1.18, p=0.57) also indicated no significant association of CASP10 1228G>A polymorphism with breast cancer (Figure 2). Sensitivity analysis performed after omitting each single study showed no statistically significant influence (Figure 3).

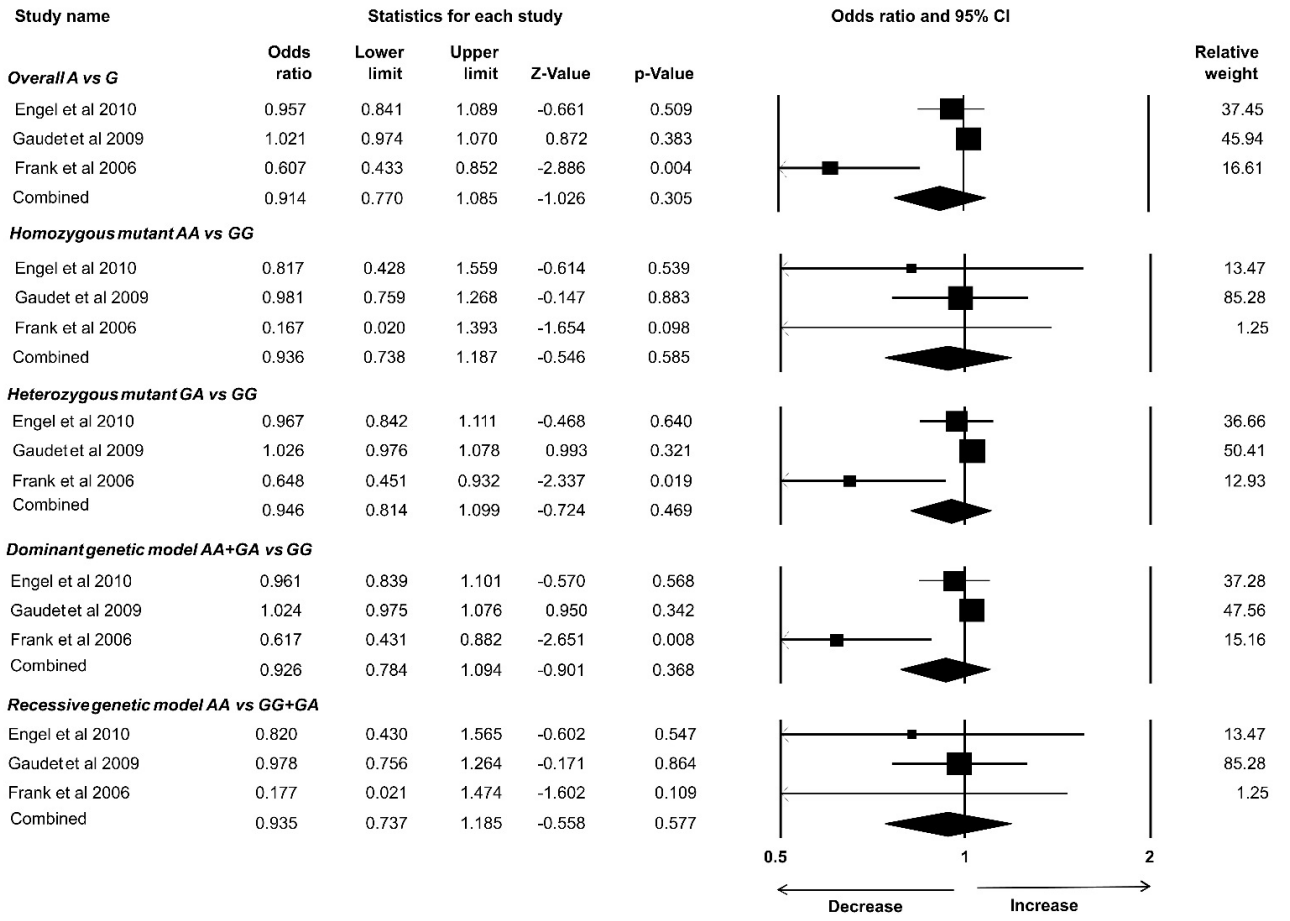

Figure 2: Forest plot of CASP10 1228G>A polymorphism in association with breast cancer risk: Meta-analysis was performed using previously published literatures using Comprehensive meta-analysis V3 software (CMA V3). Random or fixed model used for the analysis for calculating the combined effect of the studies.

Discussion

In the pooled study of 31,300 Breast Cancer (BC) cases and 34,331 healthy controls, we demonstrated that minor allele A of caspase-10 (1228G>A) was not associated with BC (OR=0.91, 95%CI=0.77-1.08). There was heterogeneity between the studies, but the source was unknown. Sensitivity analysis was performed by omitting any single study, but no significant influence was found.

Caspases are highly specific proteolytic proteins that cleave substrates in a caspase-cascade manner in apoptotic cells and during development processes. The apoptotic pathway involving caspases is highly conserved in eukaryotes. Caspase activation in apoptosis-committed cells leads to enzymatic caspase cascade which degrade important structural proteins, proteins responsible for DNA-repair. However, alternation in this process results into diverse disease conditions [7]. Caspase-10 one of the key mediators in apoptosis contained several functional polymorphisms which may cause cancer risk [9,18,19]. The polymorphism caspase-10 1228G>A is found five amino acid upstream of the cleavage site and seven amino acids downstream of the conserved active-site motif (QACXG penta peptide) which contains the catalytic cysteine residue [20]. The variation for G to A at 1228 position affects the caspase cleavage and activation. The G to A variation is shown to cause BC risk; however, there were inconsistencies in the study.

Our study could not find any association of caspase-10 (1228G>A) with BC specifically in Caucasian. There were limitations regarding this meta-analysis should be addressed. Firstly, the study included for the analysis was few even though the sample size was large. Secondly, all the studies included were only of European origin, therefore we could not conclude the role of A minor allele in other ethnic population. Thirdly, the source of heterogeneity among studies could not be address. Fourthly, the case and control were included based on well-defined inclusion criteria; however, other factors not included may have influenced our findings.

Study name	Statistics with study removed					Odds ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Overall A vs G						
Engel et al 2010	0.810	0.488	1.344	-0.816	0.414	
Gaudet et al 2009	0.784	0.503	1.221	-1.076	0.282	
Frank et al 2006	1.013	0.970	1.059	0.595	0.552	
Combined	0.914	0.770	1.085	-1.026	0.305	
Homozygous mutant AA vs GG						
Engel et al 2010	0.956	0.741	1.234	-0.345	0.730	
Gaudet et al 2009	0.713	0.384	1.324	-1.070	0.285	
Frank et al 2006	0.957	0.753	1.215	-0.363	0.716	
Combined	0.936	0.738	1.187	-0.546	0.585	
Heterozygous mutant GA vs GG						
Engel et al 2010	0.846	0.543	1.318	-0.739	0.460	
Gaudet et al 2009	0.822	0.559	1.208	-0.999	0.318	
Frank et al 2006	1.019	0.972	1.068	0.776	0.438	
Combined	0.946	0.814	1.099	-0.724	0.469	
Dominant genetic model AA+GA vs GG						
Engel et al 2010	0.821	0.501	1.344	-0.786	0.432	
Gaudet et al 2009	0.795	0.517	1.222	-1.046	0.296	
Frank et al 2006	1.017	0.971	1.065	0.700	0.484	
Combined	0.926	0.784	1.094	-0.901	0.368	
Recessive genetic model AA vs GG+GA						
Engel et al 2010	0.954	0.739	1.231	-0.362	0.717	
Gaudet et al 2009	0.720	0.388	1.336	-1.042	0.297	
Frank et al 2006	0.955	0.752	1.212	-0.381	0.703	
Combined	0.935	0.737	1.185	-0.558	0.577	

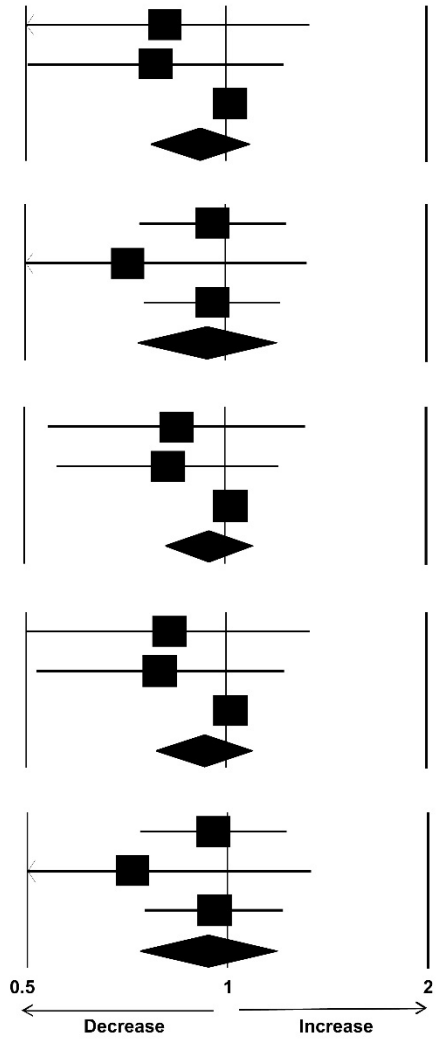

Figure 3: Sensitivity analysis (leave-one-out) of meta-analysis of risk of breast cancer women with CASP10 1228G>A polymorphism: Sensitivity analysis was performed by removing one study each time using Comprehensive meta-analysis V3 software (CMA V3). Either random or fixed model was used for the analysis for calculating the combined effect of the studies. Sensitive analysis results showed no effect of single study on odds ratio.

Conclusion

In conclusion, this meta-analysis of 31,300 cases and 34,331 controls of BC suggested that caspase-10 (1228G>A) polymorphism was not associated with the disease. As there was very little study on this polymorphism, the evidence remains limited.

Therefore, there is a need of larger case-control studies of different ethnic groups along with other confounding factors in order to have conclusive result.

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Author Contributions

SC, BMK performed the inclusion of database searches, reviewed and selected eligible literature. SC, BMK and DRM analysed the data and performed the statistical analysis. SKM and SC are responsible for the concept/reagents/materials/analysis tools. SKM, SC wrote the manuscript.

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Availability of Data and Materials

All the authors confirmed the availability of data and materials.

Conflict of Interest

Authors have declared no conflict of interest.

Consent for Publication

Not applicable.

Ethics Approval

Not applicable.

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