RESEARCH ARTICLE

Specific CCND1 G870A Alleles Associated with Breast Cancer Susceptibility: a Meta-analysis of 5,528 Cases and 5,353 Controls

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Abstract

Background: The Cyclin D1(CCND1) G870A polymorphism may be associated with breast cancer, but the evidence from individual studies is inconclusive. The aim of this study was to investigate the correlation between the CCND1 G870A polymorphism and breast cancer risk in a meta-analysis. Materials and Methods: We searched Pubmed and analysed 11 articles on 5,528 cases and 5,353 controls before February 1, 2012. Results: we found there are significant association for AA versus GG and AA versus GA/GG. No significant associations were found for GA versus GG, GA/AA versus GG. There are significant association for AA versus GG ,and AA versus GA/GG in Caucasians. We didn't find any significant main effects for G870A polymorphism on breast cancer risk either in recessive or dominant models in Asians. Conclusion: This meta-analysis suggests that AA of the CCND1 G870A polymorphism is associated with breast cancer susceptibility.

Keywords: CCND1 - breast cancer - meta-analysis

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Introduction

Cyclin D1(CCND1), a member of the D-type cyclin family, is the main cyclin that regulates the G1 phase of the cell cycle. Overexpression of CCND1 promotes this phase, and disrupts normal cell cycle control, possibly accelerate the development and progression of cancer (Sutherland and Musgrove, 2002). It is reported that CCND1 was associated with colorectal cancer (Balcerczak et al., 2005; Ceschi et al., 2005), breast cancer (Ceschi et al., 2005), gastric cancer (Bizari et al., 2006), prostate cancer (Noel et al., 2010) and so on .

Cyclin D1, a protein encoded by the CCND1 gene located on chromosome 11q13, is essential for the regulation of cell proliferation, differentiation, and transcription (Chen et al., 2012). Several studies have identified a correlation between the CCND1 870A allele and an increased cancer risk, including bladder , prostate ,liver and breast cancer (Wang et al., 2002; Wang et al., 2003; Akkiz et al., 2010; Canbay et al., 2010).

To date, several studies have reported the role of the CCND1 G870A polymorphism in breast cancer risk. But the results are controversial, partially because of the possible small effect of the polymorphism on breast cancer risk. In order to estimate the overall risk of CCND1 G870A polymorphism associated with breast cancer, we conducted a meta-analysis on 11 published case-control studies of breast cancer with 5,528 breast cancer cases and 5,353 controls.

Materials and Methods

Publication search

We searched the articles using the terms "CCND1", "polymorphism" or "variation", "G870A" or "rs603965", and "breast cancer" in Medline database utilizing the PubMed engine, and all eligible studies were published before February 1, 2012. The search was limited to English-language papers. We evaluated all associated publications to retrieve the most eligible literatures. Their reference lists were hand-searched to find other relevant publications.

Inclusion criteria

The following inclusion criteria were used for the literature selection in our meta-analysis: (a) use a case-control design; (b) evaluation of the CCND1 polymorphism and breast cancer risk; (c) have available genotype frequencies for both patients and control populations; and(d) the control in the group were in agreement of Hardy-Weinberg equilibrium (HWE).

Exclusion criteria

The following exclusion criteria were set: (1) incomplete raw data; (2) repetitive reports (if more than one version of the same study was retrieved, only the most recent was used); and (3) materials and methods were not well-described and reliable.

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Table 1. Characteristics of All Eligible Studies Included in the Meta-analysis

First author	Year	Ethnicity	Total cases/controls	Genotypes distributions(case/control)			HWE
				G/G	G/A	A/ A	
Krippl	2003	Caucasian	497/498	112/116	247/265	138/117	0.151
Grieu	2003	Caucasian	339/327	90/92	158/176	79/71	0.556
Forsti	2004	Caucasian	223/298	59/91	116/146	48/61	0.862
Justenhoven	2009	Caucasian	1143/1155	224/204	492/506	277/286	0.468
Naidu	2008	Asian	230/200	58/54	103/98	69/48	0.787
Ceschi	2005	Asian	255/666	57/124	95/309	103/233	0.23
Onay a	2008	Caucasian	1228/719	335/217	573/346	314/156	0.412
Onay b	2008	Caucasian	728/687	179/195	355/334	179/143	0.999
Yaylim-Eraltan	2009	Caucasian	38/64	15/18	8/31	15/15	0.05
Canbay	2010	Caucasian	78/84	10/21	47/44	21/19	0.65
Jeon	2010	Asian	769/695	178/171	361/325	230/199	0.09

Table 2. Meta-anaylsis of the CCND1 G870A Polymorphism on Breast Cancer

Variables	n[a]	GA vs.GG		AA vs.GG		GA/AA Vs. GG		AA Vs.GA/GG	
		OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]
Total	11	1.01(0.88-1.15)	0.08[c]	1.13(1.01-1.26)	0.34	1.03(0.94-1.12)	0.1	1.12(1.02-1.22)	0.27
Ethenicities									
European	8	1.04(0.93-1.16)	0.1	1.15(0.98-1.36)	0.19	1.06(0.91-1.23)	0.06c	1.11(0.97-1.28)	0.16
Asian	3	0.90(0.68-1.21)	0.14	1.10(0.89-1.35)	0.61	1.00(0.84-1.20)	0.33	1.16(0.98-1.37)	0.5

[a]number of comparisons; [b]P value of Q-test for heterogeneity test; [c]Random-effects model was used when P value for heterogeneity test <0.05; otherwise, fix-effects model was used

Data extraction

Two investigators (Liang and Yu) extracted information independently according to the inclusion and exclusion criteria listed. When it came to conflicting evaluations, an agreement was reached after a discussion. For each study, the following data were considered: the first author's surname, years of publication ,ethnicity, HWE, and total number of cases and controls as well as numbers of cases and controls with G/G, G/A and A/A genotypes, respectively. Different ethnic descents were categorized as Caucasian, Asian. For studies including subjects of different ethnic groups, datas were extracted separately for each ethnic group whenever possible.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the CCND1 polymorphism and breast cancer risk. The pooled ORs were performed for co-dominant model (GA versus GG, and AA versus GG), dominant model (GA/AA versus GG), and recessive model (AA versus GA/ GG), respectively. In consideration of the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q statistic. If the P<0.10 of the Q-test which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by the fixed-effects model.Otherwise, the random-effects was used. Stratified analyses were also performed by ethnicity. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias .All analyses were done with Review Manage 5.0,and Stata software version 10.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A total of 11 eligible studies involving 5528 cases and 5353 controls were included in the pooled analyses (Jones et al., 1995; Grieu et al., 2003; Krippl et al., 2003; Forsti et al., 2004;Ceschi et al., 2005; Naidu et al., 2008; Onay et al., 2008; Justenhoven et al., 2009; Yaylim-Eraltan et al., 2009; Canbay et al., 2010). Table 1 presents the main characteristics of those studies. All of the eleven publications were published in English. The sample sizes ranged from 38 to 1228. Breast cancers were confirmed histologically or pathologically. The controls were mainly healthy populations. There were 3 groups of Asians, and 8 groups of Caucasians.

Meta-analysis

As shown in Table 2, there are significant association for AA versus GG (OR = 1.13, 95% CI = 1.01-1.26, $P_{heterogeneity}$=0.34), and AA versus GA/GG (OR = 1.12, 95% CI = 1.02-1.22, $P_{heterogeneity}$ =0.27). No significant associations were found for GA versus GG (OR = 1.01, 95% CI = 0.88-1.15, $P_{heterogeneity}$ =0.08), GA/AA versus GG (OR = 1.03, 95% CI = 0.94-1.12, $P_{heterogeneity}$ =0.10).

To explore the heterogeneity, we divided the studies into subgroups, Caucasian and Asian subjects, which revealed that most of the studies could not be grouped according to ethnicity. There are significant association for AA versus GG (OR = 1.15, 95% CI = 0.98-1.36, $P_{heterogeneity}$=0.19), and AA versus GA/GG (OR = 1.11, 95% CI = 0.97-1.28, $P_{heterogeneity}$ =0.16) in Caucasian. However, we didn't find any significant main effects for G870A polymorphism on breast cancer risk either in recessive or dominant models in Asians.

Publication bias

Funnel plot and Egger's test were performed to estimate the publication bias of literatures. The data suggested that there was no evidence of publication bias in CCND1 G720A polymorphism (p=0.85 for GA vs. GG; p=0.846, for AA vs. GG; p=0.856 for GA/AA vs.GG; p=0.751 for AA vs. GG/GA)

Discussion

We conducted a systematic search of the literatures and combined the available results in our meta-analysis, which is a useful strategy for evaluating genetic factors in cancer.

Overall, we found that AA genotypes of the CCND1 G870A polymorphism were significantly associated with breast cancer risk. However, we didn't find any association between GA of CCND1 G870A and breast cancer risk. In stratified analysis by ethnicity, we found that AA of CCND1 G870A was significant associated with breast cancer in Caucasians, but not in Asians. These findings indicate that the polymorphisms of A allele would promote the risk for breast cancer and the effect of A allele on the risk of breast cancer may differ by ethnicity.

Cyclin D1 exists in two isoforms: cyclin D1a and cyclin D1b. Cyclin D1b contains an altered C-terminus, characterized by 14 amino acids encoded by a read through into intron 4, with the entire exon 5 encoded sequences being replaced. Therefore, cyclin D1b lacks the residues required for nuclear export. Accordingly, cyclin D1b has been shown to be constitutively nuclear in localization, with an increased transforming capability compared with the full-length D1a, and was considered a nuclear oncoprotein (Lu et al., 2003; Solomon et al., 2003). CCND1 G870A polymorphism does not lead to an amino acid change but the 870A allele favors the production of an alternative transcript encoding cyclin D1b (Holley et al., 2005).

There are some limitations of this meta-analysis must be addressed. Firstly, in our subgroup analysis, the numbers of Asians were relatively small, not having enough statistical power to explore the real association. Secondly, only published studies were included in this meta-analysis. Therefore, publication bias may have occurred, even though the use of a statistical test did not show it.

To conclude, this meta-analysis suggests that AA of the CCND1 G870A polymorphism is associated with breast cancer susceptibility. For future association studies, strict selection of patients, well-matched controls and larger sample size will be required. Furthermore, gene-gene and gene-environment interactions should also be considered in future studies.

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