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Original Article

Association study of *CCND1* G870A polymorphism with gastric cancer risk: evidence from a meta-analysis

Xiufeng Wang[1], Li Cao[2], Fangxin Zhang[1], Xiuli Wang[3], Jiucong Zhang[1], Juhong Pei[1], Dehua Kong[1]

[1]Department of Gastroenterology, Lanzhou General Hospital of Lanzhou Military Area Command of Chinese PLA, Lanzhou 730050, China; [2]Department of Neurology, Lanzhou General Hospital of Lanzhou Military Area Command of Chinese PLA, Lanzhou 730050, China; [3]Department of Ultrasound Diagnosis, Lanzhou General Hospital of Lanzhou Military Area Command of Chinese PLA, Lanzhou 730050, China

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Abstract: Background: The correlation between *CCND1* G870A polymorphism with gastric cancer risk had studied by teams of researchers widely, but the results were inconsistent. It is necessary to conduct a meta-analysis for exploring whether really existed a relevance between them with previous studies. Methods: Electronic searching of PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), WanFang and Weipu databases was conducted for all eligible studies. And seven publications including 1,583 cases and 2,491 controls were finally collected into this meta-analysis. The heterogeneity among studies was detected by chi-square-based Q-test. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated by the fixed or random effect model for all genetic models to evaluate the effect of *CCND1* G870A polymorphism on gastric cancer. Begg's funnel plot and Egger's linear regression were used to do check whether existed publication bias. Results: The overall result showed that *CCND1* G870A polymorphism had no significant relevance with gastric cancer (OR=1.05, 95% CI=0.91-1.22). But a subgroup analysis by control source, *CCND1* G870A polymorphism was associated with a moderate increase risk of gastric cancer only in population-based group under the model of AA vs. GA + GG (OR=1.25, 95% CI=1.02-1.53). Conclusion: This meta-analysis indicates that *CCND1* G870A polymorphism with AA genotype may play a certain role in the etiology of gastric cancer.

Keywords: *CCND1,* polymorphism, gastric cancer, meta-analysis

Introduction

Gastric cancer, also called stomach cancer, is one of the most incident cancers and the third leading cause of deaths from cancer. It accounts for 8%, 9% of the total cases and deaths worldwide, respectively [1]. It has been reported that gastric cancer is more common in men and citizens at the age of 50 years or older [2]. Gastric cancer at early stage may manifest as cardiodynia, upper abdominal pain and naupathia, and it may lead to yellow skin, loss of weight, emesis, dysphagia, and defecate haemorrhage at later stage [3]. More severely, it is very easy to metastasize to other parts of the body, especially lung, liver, abdomen and lymph node. The prognosis is usually poor with less than 10% of mean 5-year survival rate around the globe. And in the United States the 5-year survival is only 28%, whereas in South Korea it is more than 65% partly because of screening efforts [4].

So far, the exact etiology of gastric cancer is still unknown. Gastric cancer is a disease caused by multiple factors [5]. Smoking [6, 7], alcohol consumption [8, 9], iodine deficiency [10], obesity [11], genetic components [12] and some dietary factors [8, 13, 14] have been confirmed to affect the risk of gastric cancer.

G1/S-specific cyclin-D1 (*CCND1*) is a protein that is encoded by *CCND1* gene located on 11q13 in humans. It is a member of the highly conservative cyclin family which exist the whole cell cycle and their protein abundance alter periodically. Cyclin acts as a mediator of cyclin-dependent kinase (CDK) and composes a complex with a regulatory subunit of CDK4 or CDK6 whose activity is necessary for cell cycle G1/S

transition [15, 16]. *CCND1* has been indicated to interact with tumor suppressor protein Rb, and the expression of *CCND1* gene is regulated positively by Rb. Over-expression and mutations of the gene may change the process of cell cycle and thus result in the occurrence of cancer [17]. Studies have reported a G to A polymorphism at nucleotide 870, codon 242 in exon 4 (G870A) of *CCND1* gene is involved in a variety of cancers, such as lung cancer, colorectal cancer, head and neck cancer, ovarian cancer, bladder cancer, cardiac and non-cardiac gastric cancer [18-23]. However, a consistent conclusion has not been reached among the published studies. We therefore proceeded a systematic meta-analysis to quantitatively evaluate the association of *CCND1* G870A polymorphism with gastric cancer risk.

Materials and methods

Searching

In PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), WanFang and Weipu databases, we searched all relevant publications using a series of key words as "cyclin-D1" or "*CCND1*", "polymorphism" or "variant" or "polymorphisms" or "polymorphic", and "gastric cancer" or "stomach cancer". Language, sample size and publication date were not restricted in the studies. All available publications were screened and their references were also retrieved for more other useful studies.

Inclusion criteria

In order to scientifically and comprehensively assess the significance of *CCND1* G870A polymorphism in gastric cancer, we put forward the following inclusion criteria for all eligible studies: a) it evaluates the effect of *CCND1* G870A polymorphism on gastric cancer risk; b) applying a case-control design; c) supplying detailed information about genotyping; d) possessing adequate and available genotype data for the calculation of odd ratio (OR) with 95% confidence interval (CI). If two or multiple studies were reported by the same writers, either one with the largest sample size or the most recent study was incorporated in the meta-analysis. Only case reports, review articles, editorials and letters would not be included.

Data abstraction

Using a standard reporting form, two of the authors abstracted the following variables separately: first author's name, date of publication, nation, ethnicity, control source (categorized as hospital- and population-based), genotyping method, case and control number, genotype frequency and *P* value for control subjects in Hardy-Weinberg equilibrium (HWE). If there appeared different extraction results, the disagreements were adjudicated in all reviewers until a consensus was generated.

Statistical analysis

All statistical analyses were completed with the aid of STATA software (V.12.0, STATA Corp). The correlation of *CCND1* G870A polymorphism with gastric cancer risk was mainly displayed by the pooled OR with corresponding 95% CI under the five genetic contrasts including AA vs. GG, AA + GA vs. GG, AA vs. GA + GG, Allele A vs. Allele G, and GA vs. GG. In order to examine whether existed source-specific influence, we carried out a subgroup analysis based on source of control. We detected the heterogeneity among studies using Q test. When the *P* value less than 0.1 indicated a significant heterogeneity, the pooled OR with 95% CI was calculated by the random-effect model (DerSimonian and Laird method); if not, the fixed-effect model (Mantel-Haenszel method) was introduced. Sensitivity analysis was conducted though removing one-study in turn to evaluate the influence of each study on the combined results. Publication bias was checked by Begg's funnel plot, and if the plot was asymmetric, there might be a possible publication bias. Additionally, Egger's test was also used to statistically evaluate publication bias, with the significance level at $P<0.05$.

Results

Study features

According to the selection criteria, 58 publications were identified though computerized searching. As displayed in **Figure 1**, due to duplicates and obvious irrelevant information, 23 studies were excluded and 35 were further assessed. There were 28 articles were precluded for only case reported (8), unrelated SNPs (11) and no genotype frequency (9). At the end, seven articles in total were included for quantitative synthesis in the meta-analysis [23-29].

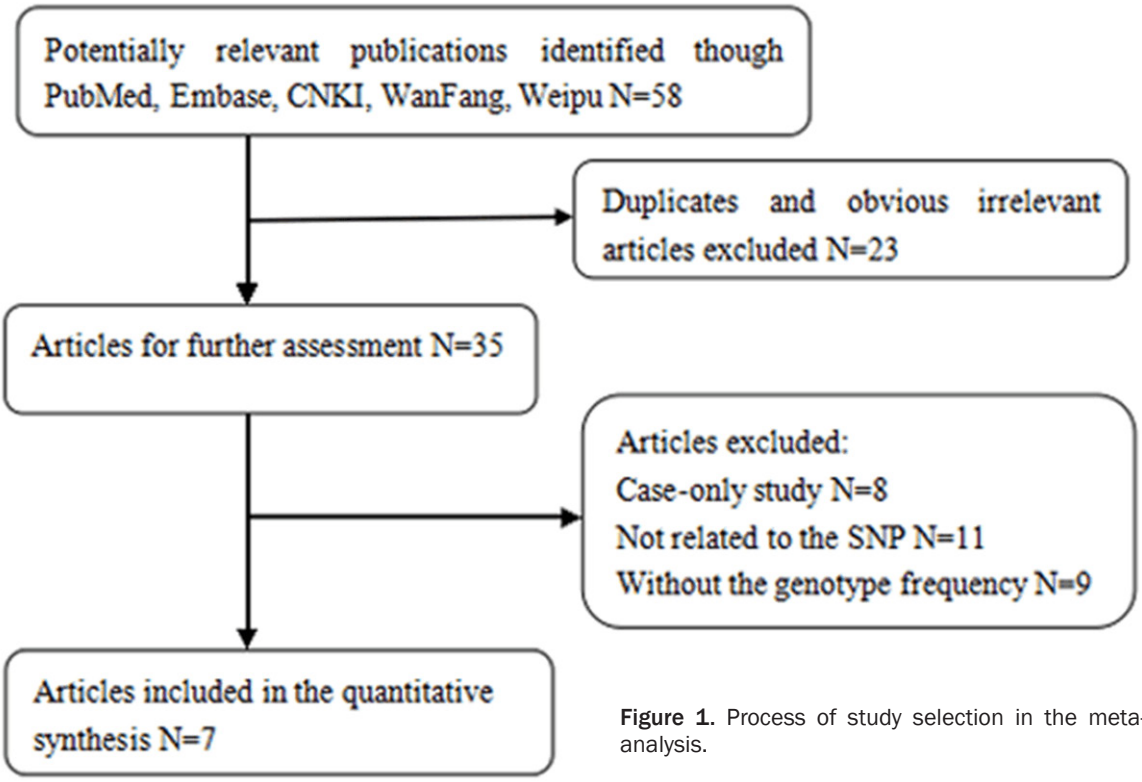

Figure 1. Process of study selection in the meta-analysis.

Among the seven included studies, six were published in English [23, 24, 26-29] and only one in Chinese [25]; six studies took Asians as research subjects [24-29] and one study discussed Caucasians [23]; three studies were conducted in hospital-based group [23, 27, 29] and the other four in population-based group [24-26, 28]. **Table 1** summarized the primary features of each included study and a total of 1,583 cases and 2,491 controls were gathered for further calculation and evaluation.

Meta-analysis results

Overall, no significant association between *CCND1* G870A polymorphism with gastric cancer susceptibility was observed. As for the subgroup analysis stratified by source of control, AA genotype of *CCND1* G870A polymorphism was associated with an increased risk of gastric cancer in population-based group (AA vs. GA + GG: OR=1.25, 95% CI=1.02-1.53) (**Table 2**; **Figure 2**).

Sensitivity analysis

To ensure the stability of overall results, we carried out the sensitivity analysis with one study deleted at a time. The final OR did not present a remarkable alteration (data not shown), so our meta-analysis results were robust.

Publication bias test

Potential publication bias was checked by Begg's funnel plot and Egger's test. None of the funnel plots under each genetic contrast appeared asymmetrical, as one displayed in **Figure 3**. Moreover, the *P* values of Egger's test were all larger than 0.05, which further verified a less apparent publication bias.

Discussion

Accept some environmental factors, certain genetic backgrounds may exert influence on the pathogenesis of gastric cancer. These genetic factors independently or their interactions with carcinogenic agents outside contributes to a series of mutations in related genes of body tissues, which causes the abnormal proliferation of cells and the generation of tumors. Studies have indicated polymorphisms within tumor suppressor genes, enzyme genes and DNA repair genes can make individuals at a high risk of gastric cancer [30-32].

Table 1. Summary of main characteristics on included studies

Reference	Year	Nation/Ethnicity	Control source	Genotyping method	Cases						Controls						*P* (HWE)
					Samples	GG	GA	AA	G	A	Samples	GG	GA	AA	G	A	
Geddert [23]	2005	Germany/Caucasian	HB	PCR	191	29	133	29	191	191	253	63	136	54	262	244	0.224
					95	26	55	14	107	83	253	63	136	54	262	244	0.224
Song [28]	2007	Korea/Asian	PB	PCR-SSCP	253	71	125	57	267	239	442	102	226	114	430	454	0.623
Kuo [24]	2014	China/Asian	PB	PCR-RFLP	358	46	178	134	270	446	358	59	212	87	330	386	0.0003
Tahara [27]	2009	Japan/Asian	HB	PCR-RFLP	11	5	3	3	13	9	359	98	180	81	376	342	0.924
					371	95	188	88	378	364	359	98	180	81	376	342	0.924
Jia [29]	2008	China/Asian	HB	PCR-RFLP	159	31	81	47	143	175	162	16	85	61	117	207	0.081
Wang [25]	2003	China/Asian	PB	PCR-SSCP	58	12	26	20	50	66	122	25	68	29	118	126	0.200
Zhang [26]	2003	China/Asian	PB	PCR-SSCP	87	19	40	28	78	96	183	38	102	43	178	188	0.118

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; PCR-SSCP: PCR-single strand conformation polymorphism; HWE: Hardy-Weinberg equilibrium.

Table 2. The association between *CCND1* G870A polymorphism and gastric cancer risk

		AA vs. GG		AA + GA vs. GG		AA vs. GA + GG		Allele A vs. Allele G		GA vs. GG	
		OR/95% CI	P/ heterogeneity	OR/95% CI	P/ heterogeneity	OR/95% CI	P/ heterogeneity	OR/95% CI	P/ heterogeneity	OR/95% CI	P/ heterogeneity
Control source	Hospital-based	0.94/0.74-1.19	0.772	1.01/0.88-1.16	0.815	0.86/0.70-1.07	0.584	0.97/0.87-1.09	0.759	1.02/0.87-1.21	0.661
	Population-based	1.07/0.85-1.34	0.513	0.99/0.86-1.14	0.930	1.25/1.02-1.53	0.110	1.05/0.94-1.18	0.371	0.96/0.81-1.14	0.967
Total		1.01/0.85-1.18	0.790	1.00/0.91-1.10	0.980	1.05/0.91-1.22	0.064	1.01/0.94-1.10	0.655	0.99/0.88-1.12	0.938

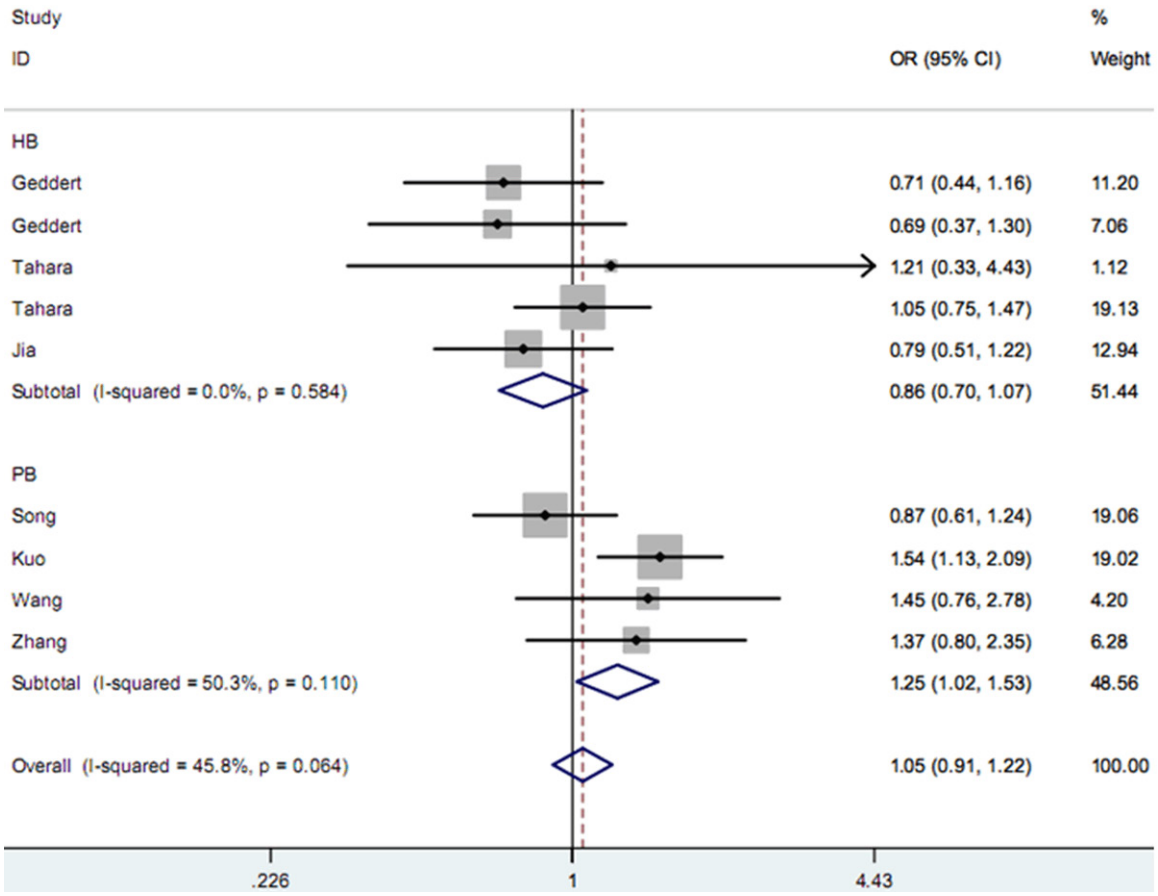

Figure 2. Forest plot of *CCND1* G870A polymorphism and gastric cancer.

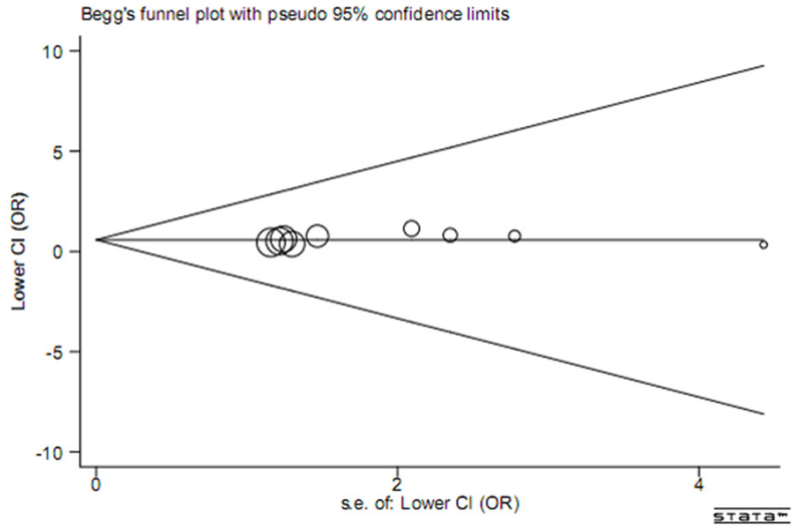

Figure 3. Begg's funnel plot for publication bias.

It is widely accepted that the imbalance of cell growth cycle plays a critical role in the occurrence and progression of tumors. As an important regulator of normal cell cycle, *CCND1* is likely to mediate susceptibility to various tumors. The interaction of *CCND1* and CDK mediates proliferation, differentiation, and death process of cells, and participates in DNA duplicate and repair, phosphorylation of histone H1 and protein retinoblastoma (pRB). The over-expression of *CCND1* is able to advance the phosphorylation of pRB, so that it accelerates the transition of G1 stage to S stage of cells and the process of DNA replication [33]. In esophagus cancer, breast cancer and colorectal cancer, overexpression of *CCND1* always indicates a high recurrence rate and a poor outcome [34-37]. Therefore,

CCND1 can be used as a molecular maker of cancerization [38]. The polymorphisms of *CCND1* gene are also concerned widely by explorers, especially a mutant from G to A in the position of 870 base pair. A study from Aytekin et al. draw a conclusion that *CCND1* G870A polymorphism was related with the risk of papillary thyroid cancer, even worse for the old people (more than 45 years old) and females in the Turkish population [39]. A meta-analysis was conducted to explore the effect of *CCND1* polymorphism on head and neck cancer, the result showed that carrying A allele and AA genotype of *CCND1* G870A polymorphism may have susceptibility to head and neck cancer development in smokers [40].

To date, the mechanism of *CCND1* G870A polymorphism affecting the onset of gastric cancer still remains unclear. One of the hypotheses is that this polymorphism may influence the types and characters of splicing in *CCND1* mRNA [33]. Several studies have investigated the association of *CCND1* G870A polymorphism with gastric cancer susceptibility, however, they have put forward inconsistent results, indicating different effects of sample size, genetic background and other confounding factors on the cancer. A study in Taiwan population, Kuo et al. gained the result that people with AG or GG genotype of *CCND1* G870A had 0.55- and 0.51-fold risk of suffering from gastric cancer compared with those with AA genotype and AA genotype might act as a risk factor for gastric cancer [24]. Similarly, in northern Chinese, smokers carrying AA genotype were at a high risk of developing gastric cancer [25, 26]. In contrast, some other studies failed to verify the significant correlation both in Asians and Caucasians [23, 27, 28]. Jia et al. specifically studied the *CCND1* G870A polymorphism involved in non-cardiac gastric cancer and found the risk of non-cardiac gastric cancer for Chinese people with GG genotype was 2.8 and 1.4 times that of those with AA and GA genotypes, respectively. Moreover, in the stratified analyses, the cancer risk caused by GG genotype was more apparent in subjects aged 60 years and those positive for Helicobacter pylori (H. pylori) infection [29]. Based on the previous publications, our meta-analysis suggested an increased risk of gastric cancer associated with AA genotype of *CCND1* G870A polymorphism, which needs a further verification.

Gender and smoking status may have some certain influence on the susceptibility to gastric cancer, as has been indicated in studies described above [23, 26, 29]. However, in present meta-analysis, we only discussed a single genetic factor and ignored other potential confounding factors, which may lead to a less robust result. In addition, the number of included studies is relatively small and the statistical evidence may not be enough for the verification of the meta-analysis findings.

Taken together, the results of this meta-analysis indicated a significant relationship between *CCND1* G870A polymorphism and risk of gastric cancer. Due to some inevitable limitations, our findings need to be further checked by more studies with larger sample sizes and considering the interactions of genetic polymorphisms and external confounding factors.

Disclosure of conflict of interest

None.

Address correspondence to: Xiuli Wang, Department of Gastroenterology, Lanzhou General Hospital of Lanzhou Military Area Command of Chinese PLA, Lanzhou 730050, China. E-mail: xiuliwiang@163.com

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