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ORIGINAL RESEARCH

Association between cyclin D1 G870A polymorphism and hepatocellular carcinoma risk: a meta-analysis

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Background: Cyclin D1 (CCND1) G870A polymorphism may be associated with hepatocellular carcinoma (HCC) risk, but the results of previous studies were inconsistent. Available evidence was meta-analyzed to assess their potential association.

Methods: Databases PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature database, China National Knowledge Infrastructure, and Google Scholar were systematically searched. Meta-analyses were performed to investigate the association of G870A polymorphism with HCC risk by calculating odds ratios (ORs) and 95% confidence intervals (CIs) from the data of relevant case–control studies.

Results: Results of this meta-analysis of six case–control studies involving 1,030 cases and 1,683 controls indicate that G870A polymorphism was not associated with HCC risk in any of the five genetic models tested (recessive model: AA vs GG + AG: OR =1.38, 95% CI =0.95–2.00, P=0.09; dominant model: AG + AA vs GG: OR =1.38, 95% CI =0.87–2.20, P=0.17; homozygous model: AA vs GG: OR =1.60, 95% CI =0.87–2.94, P=0.13; heterozygous model: AG vs GG: OR =1.24, 95% CI =0.86–1.79, P=0.25; allelic model: A vs G: OR =1.30, 95% CI =0.95–1.80, P=0.10). Subgroup analyses according to ethnicity showing marginally significant association between this single nucleotide polymorphism and HCC risk indicate that G870A may be significantly associated with HCC risk in Caucasian populations (recessive model: AA vs GG + AG: OR =2.34, 95% CI =1.60–3.42, P<0.0001; dominant model: AG + AA vs GG: OR =2.44, 95% CI =1.19–4.97, P=0.01; homozygous model: AA vs GG: OR =3.42, 95% CI =1.80–6.50, P=0.0002; allelic model: A vs G: OR =2.06, 95% CI =1.31–3.24, P=0.002), but not in Asian populations.

Conclusion: Available evidence suggests that no significant association between G870A polymorphism and HCC risk was found in either total populations or Asian populations. However, significant association was found in Caucasian populations. These results should be verified and extended in further detailed and well-designed studies involving larger, multiethnic samples.

Keywords: cyclin D1 G870A, single nucleotide polymorphism, hepatocellular carcinoma, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is considered as the fifth most common neoplasm worldwide, with an increasing incidence and a low survival. It is also the second leading cause of cancer death in males and the sixth leading cause of cancer death in females around the globe.[1,2] Highly aggressive and poor prognosis in terrible mortality are the predominant characteristics of HCC throughout the world. Therefore, HCC is a serious fatal disease and has caused serious damages to human health. As a complex

and heterogeneous process, the pathogenesis of HCC is not completely understood. Previous studies have established that the development of HCC is linked to interactions of various risk factors, such as chronic infection with hepatitis B virus (HBV) or hepatitis C virus, liver cirrhosis, chronic alcohol use, and exposure to aflatoxin.[3–5] Furthermore, recent studies, which highlighted the relationship between gene polymorphisms and the development and progression of HCC, have proposed that genetic factors may contribute to carcinogenesis.[6,7]

Cyclin D1 (CCND1) is a major regulatory protein that plays a specific role in the cell cycle, promoting the G1 to S phase transition of the cell cycle by binding and activating cyclin-dependent kinase 4 (CDK4) or cyclin-dependent kinase 6 (CDK6).[8,9] Overexpression or disordered regulation of CCND1 is a driving force in certain cancers of humans, such as non-small-cell lung cancer[10] and breast cancer.[11] Due to the eventfulness of CCND1 in the cell division, *CCND1* gene single nucleotide polymorphism (SNP) has been investigated in various cancers. G870A (rs603965) is one of the most frequent SNPs in the *CCND1* gene, located at codon 242 in the splice donor region of exon 4.[12]

Numerous case–control studies have investigated a potential association between CCND1 G870A polymorphism and risk of carcinomas. Most of these studies have demonstrated that G870A may be associated with decreased risk of carcinomas, while some failed to detect any significant association.[13–19] Similarly, the available case–control studies investigating the possible association between G870A and HCC risk have given inconsistent results.[20,21] Related meta-analyses have attempted to synthesize the available evidence on these associations.[22,23] Unfortunately, the results of these studies were inconsistent due to small sample sizes involved. Thus, we conducted a meta-analysis involving relevant literature up to date with a larger sample size to provide more comprehensive and reliable insights into investigating the possible associations between G870A polymorphism and HCC risk.

Methods
Search strategy
The databases PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature database, China National Knowledge Infrastructure, and Google Scholar were systematically searched up to March 15, 2016, to identify all clinical and experimental case–control studies examining associations between G870A polymorphism and HCC risk, using the following search strategy: "Cyclin D1", "CCND1",

"G870A", or "rs603965"; "hepatocellular carcinoma", "liver cancer", or "HCC"; and "polymorphism", "polymorphisms", "SNP", "variant", "variation", "mutation", "genotype", or "genetic". Reference lists in identified articles and reviews were also searched manually to identify additional eligible studies.

Inclusion criteria
Studies included in the meta-analysis were required to meet the following criteria: 1) should have assessed the association of G870A polymorphism with HCC risk in humans, 2) should have had case–control design, 3) should be available as full text, 4) should have contained sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI), including genotype frequencies, and 5) should have been published in English or Chinese language. If multiple publications reported data for the same study sample, only the study with the largest sample size was included.

Data extraction
Two authors (Tao Luo and Shao-Liang Zhu) independently reviewed and extracted the following data from all the included studies: first author's family name, year of publication, country or district, ethnicity, genotyping methods, total numbers of cases and controls, genotype frequencies in cases and controls, and the *P*-value associated with Hardy–Weinberg equilibrium (HWE) in controls. Discrepancies were resolved by discussion until consensus was achieved.

Statistical analysis
All statistical tests for this meta-analysis were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and Stata 12.0 (StataCorp LP, College Station, TX, USA).

The association between G870A polymorphism and HCC risk was estimated for each polymorphism in different comparison models, including recessive model (AA vs GG + AG), dominant model (AG + AA vs GG), homozygote model (AA vs GG), heterozygote model (AG vs GG), and allelic model (A vs G) in cases and controls by calculating unadjusted ORs with CIs. Significance of pooled ORs was determined using the Z-test, and the P-value <0.05 was considered significant. Meta-analysis was conducted using a fixed-effect model (the Mantel–Haenszel method) when $P>0.10$ for the Q-test, which indicates lack of heterogeneity among the included studies;[24] otherwise, a random-effect model (the DerSimonian–Laird method) was used.[25] To explore the sources of heterogeneity among studies, we performed subgroup analyses according to ethnicity. HWE in the

control group was assessed using Fisher's exact test with $P<0.05$ considered significant.

Publication bias was assessed using Begg's funnel plot and Egger's weighted regression, with $P<0.05$ considered significant.

Results

Description of included studies

Figure 1 is a flowchart illustrating the search and study selection criteria. A total of 936 potentially relevant articles published up to March 15, 2016, were systematically identified in database searches. Of these, we excluded 923 studies based on the review of titles and abstracts. An additional seven studies were excluded because they were reviews (n=3), meta-analyses (n=3), or did not provide usable data (n=1). As a result, six studies reporting the relationship between G870A polymorphism and HCC risk were included in this meta-analysis involving five English[20,21,26–28] and one Chinese[29] articles. Thus, a total of six divided case–control design comparisons involving 1,030 cases and 1,683 controls were finally included in the meta-analysis. Of all the eligible studies, four (including 780 HCC cases and 1,343 controls) were conducted in Asian populations,[21,26,27,29] and two (including 250 HCC cases and 340 controls) were in Caucasian populations.[20,28] The principal characteristics of the recruited studies are presented in Table 1. The distribution of genotypes in controls was consistent with HWE ($P>0.05$) in all but one study.[28]

Results of meta-analysis

The main meta-analysis results of the association between G870A polymorphism and HCC risk are shown in Table 2.

Pooled data from the entire population of 1,030 cases and 1,683 controls showed no significant association between
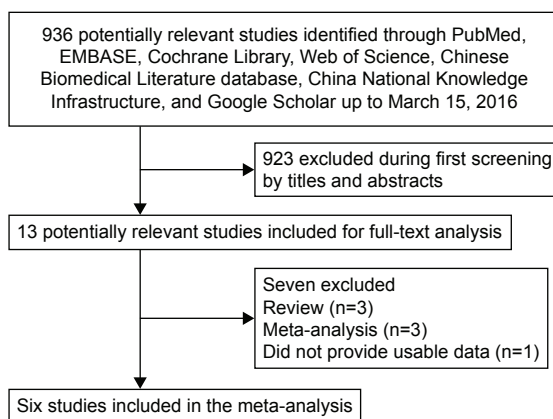
Table 1 Principal characteristics of studies in the meta-analysis

References	Year	Country/district	Ethnicity	Genotyping method	Cases/ controls	Number of cases			Allele frequencies of cases, n (%)		Number of controls			Allele frequencies of controls, n (%)		P_{HWE}
						GG	AG	AA	G	A	GG	AG	AA	G	A	
Zhang et al[26]	2002	Taiwan	Asian	PCR	97/35	9	50	38	68 (35.1)	126 (64.9)	3	19	13	25 (35.7)	45 (64.3)	0.462
Zhu et al[29]	2007	People's Republic of China	Asian	PCR–RFLP	225/428	52	118	55	222 (49.3)	228 (50.7)	73	229	126	375 (43.8)	481 (56.2)	0.078
Akkiz et al[20]	2010	Turkey	Caucasian	PCR–RFLP	160/160	38	69	53	145 (45.3)	175 (54.7)	56	73	31	185 (57.8)	135 (42.2)	0.420
Hu et al[21]	2014	People's Republic of China	Asian	PCR–RFLP	220/220	32	119	69	183 (41.6)	257 (58.4)	45	124	51	214 (48.6)	226 (51.4)	0.079
Zeng et al[27]	2015	People's Republic of China	Asian	RT-PCR	238/660	51	120	67	222 (46.6)	254 (53.4)	153	331	176	637 (48.3)	683 (51.7)	0.938
Elkhashab et al[28]	2015	Egypt	Caucasian	PCR–RFLP	90/180	18	37	35	73 (40.6)	107 (59.4)	85	61	34	231 (64.2)	129 (35.8)	0.001

Abbreviations: HWE, Hardy–Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT, real time.

936 potentially relevant studies identified through PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature database, China National Knowledge Infrastructure, and Google Scholar up to March 15, 2016

923 excluded during first screening by titles and abstracts

13 potentially relevant studies included for full-text analysis

Seven excluded
Review (n=3)
Meta-analysis (n=3)
Did not provide usable data (n=1)

Six studies included in the meta-analysis

Figure 1 Flowchart of study selection for meta-analysis.

Table 2 Meta-analysis of the association of CCND1 G870A polymorphism with HCC risk

Comparison	Group and subgroups	Sample size (n)		Test of heterogeneity		Analysis model	Test of association		
		Case	Control	P-value	I² (%)		OR	95% CI	P-value
Recessive model	Overall	1,030	1,683	0.002	74	Random	1.38	0.95–2.00	0.09
(AA vs GG + AG)	Asian	780	1,343	0.14	46	Fixed	1.07	0.80–1.43	0.66
	Caucasian	250	340	0.47	0	Fixed	2.34	1.60–3.42	<0.0001
Dominant model	Overall	1,030	1,683	0.0002	79	Random	1.38	0.87–2.20	0.17
(AG + AA vs GG)	Asian	780	1,343	0.09	53	Random	1.02	0.70–1.48	0.93
	Caucasian	250	340	0.06	71	Random	2.44	1.19–4.97	0.01
Homozygous	Overall	517	846	<0.0001	83	Random	1.60	0.87–2.94	0.13
model (AA vs GG)	Asian	373	640	0.03	67	Random	1.07	0.63–1.81	0.81
	Caucasian	144	206	0.16	49	Fixed	3.42	1.80–6.50	0.0002
Heterozygous	Overall	713	1,252	0.02	62	Random	1.24	0.86–1.79	0.25
model (AG vs GG)	Asian	551	977	0.29	21	Fixed	0.99	0.74–1.32	0.95
	Caucasian	162	275	0.09	65	Random	1.94	0.96–3.93	0.06
Allelic model	Overall	2,060	3,366	<0.00001	86	Random	1.30	0.95–1.80	0.10
(A vs G)	Asian	1,560	2,686	0.04	64	Random	1.04	0.82–1.31	0.77
	Caucasian	500	680	0.06	72	Random	2.06	1.31–3.24	0.002

Abbreviations: CCND1, cyclin D1; CI, confidence interval; HCC, hepatocellular carcinoma; OR, odds ratio.

G870A polymorphism and HCC risk in any of the five genetic models tested (recessive model: AA vs GG + AG: OR =1.38, 95% CI =0.95–2.00, P=0.09; dominant model: AG + AA vs GG: OR =1.38, 95% CI =0.87–2.20, P=0.17; homozygous model: AA vs GG: OR =1.60, 95% CI =0.87–2.94, P=0.13; heterozygous model: AG vs GG: OR =1.24, 95% CI =0.86–1.79, P=0.25; allelic model: A vs G: OR =1.30, 95% CI =0.95–1.80, P=0.10; Figure 2).

However, subgroup analyses according to ethnicity, marginally significant association between G870A polymorphism, and HCC risk indicate that G870A may be significantly associated with HCC risk in Caucasian populations (recessive model: AA vs GG + AG: OR =2.34, 95% CI =1.60–3.42, P<0.0001; dominant model: AG + AA vs GG: OR =2.44,

95% CI =1.19–4.97, P=0.01; homozygous model: AA vs GG: OR =3.42, 95% CI =1.80–6.50, P=0.0002; allelic model: A vs G: OR =2.06, 95% CI =1.31–3.24, P=0.002), but not in Asian populations (recessive model: AA vs GG + AG: OR =1.07, 95% CI =0.80–1.43, P=0.66; dominant model: AG + AA vs GG: OR =1.02, 95% CI =0.70–1.48, P=0.93; homozygous model: AA vs GG: OR =1.07, 95% CI =0.63–1.81, P=0.81; heterozygous model: AG vs GG: OR =0.99, 95% CI =0.74–1.32, P=0.95; allelic model: A vs G: OR =1.04, 95% CI =0.82–1.31, P=0.77).

Sensitivity analysis

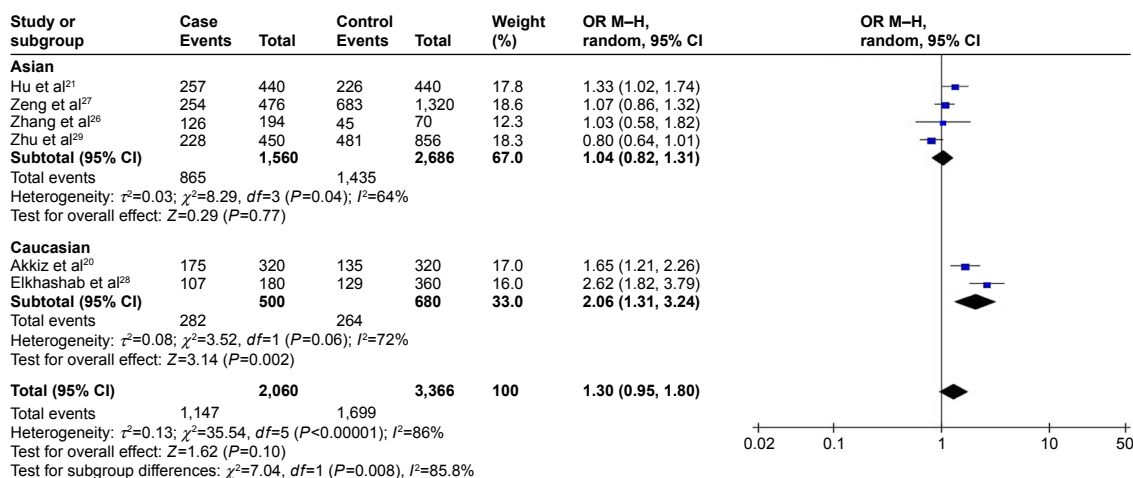Sensitivity analysis of the G870A meta-analysis was performed by excluding a single individual study each time to

Figure 2 Forest plot describing the association of the CCND1 G870A polymorphism with HCC risk according to the allele model (A vs G).
Abbreviations: CCND1, cyclin D1; CI, confidence interval; HCC, hepatocellular carcinoma; M–H, Mantel–Haenszel; OR, odds ratio.
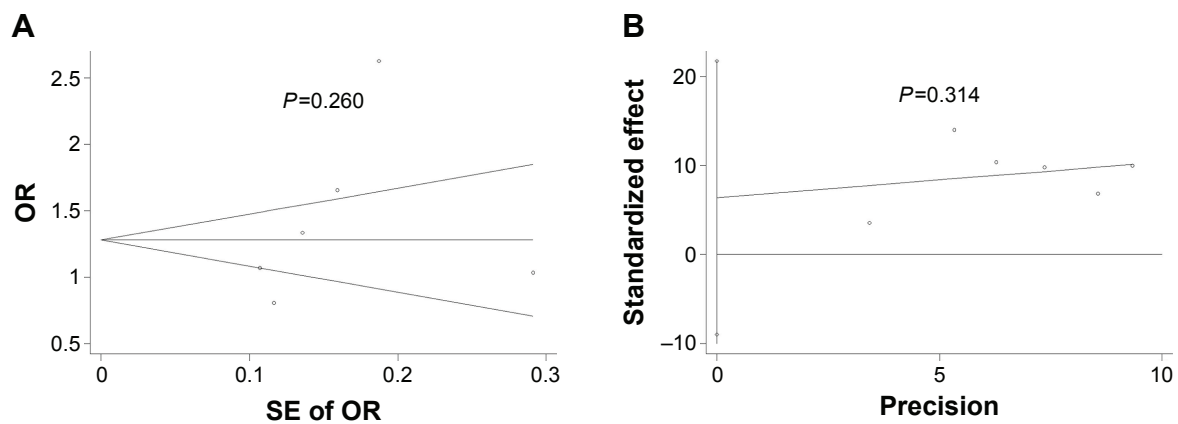
A

B

Figure 3 Plots to assess the risk of publication bias in the analysis of the association between CCND1 G870A polymorphism and HCC risk according to the allelic model (A vs G).
Notes: Begg's funnel plot with psuedo 95% confidence limits (**A**). Egger's publication bias plot (**B**).
Abbreviations: CCND1, cyclin D1; HCC, hepatocellular carcinoma; OR, odds ratio; SE, standard error.

reflect the influence to the overall ORs. Excluding the study by Zhu et al[29] led to a statistically significant result in the recessive model (AA vs GG + AG: OR =1.57, 95% CI =1.11–2.24, P=0.01), dominant model (AG + AA vs GG: OR =1.64, 95% CI =1.07–2.52, P=0.02), homozygote model (AA vs GG: OR =2.01, 95% CI =1.16–3.49, P=0.01), heterozygote model (AG vs GG: OR =1.42, 95% CI =1.01–1.99, P=0.04), and allele model (A vs G: OR =1.45, 95% CI =1.06–1.99, P=0.02). Therefore, our meta-analysis results should be interpreted with caution.

Publication bias

The risk of publication bias in this meta-analysis was assessed by generating Begg's funnel plots and performing Egger's test. Applying the allelic model (A vs G) to data from the total populations, we observed no obvious asymmetry in Begg's funnel plots (Figure 3A and B) and obtained nonsignificant P-values in Egger's test for the SNP (allele model: G vs A: t=1.15, P=0.314).

Discussion

CCND1 appears to play an important role in numerous types of cancers, where it modulates the key process during G1 to S phase transition of the cell cycle by binding and activating CDK4 or CDK6. Many studies have investigated G870A SNP in CCND1 and its potential associations with HCC risk and progression, but the results are conflicting. Therefore, we meta-analyzed the available literature as possible as we can to provide more precise estimation of the association.

The study by Elkhashab et al[28] demonstrated that SNP of G870A among the Egyptian population was associated with increased risk of HCC. The results of Akkiz et al[20]

indicated that the G870A polymorphism might be the genetic susceptibility that influences hepatocellular carcinogenesis within the Turkish population studied. Hu et al[21] suggested that the G870A polymorphism might play a role in the development of HCC among HBsAg-positive individuals in the Chinese population. Zhu et al[29] deduced that G870A was concerned with HCC risk only in females. However, the study by Zeng et al[27] found that the G870A genotype had no association with the susceptibility of HBV-related HCC in the Chinese cohort. Zhang et al[26] speculated that CCND1 genotype frequencies were similar in cases and controls and were not associated with susceptibility to the development of HCC. Two related meta-analyses by Pabalan et al[30] and Chen et al[23] drew a semblable conclusion that the G870A polymorphism conferred susceptibility to the development of cancers or digestive tract cancers. Zhao et al[22] revealed a significant relationship between the G870A polymorphism and HCC risk in the overall populations. Nevertheless, the meta-analysis by Zhao et al[22] contained a study[31] investigating the CCND1 polymorphism and onset of hepatoblastoma, instead of HCC, which might lead to an imprecision of the results.

As far as we know, this article is a meta-analysis of the comprehensive assessment that focuses only on the relationship between G870A polymorphism and HCC risk. Compared with those previous meta-analyses, the current one contained three more case–control studies involving 533 cases and 1,268 controls. The current work contained a total of six case–control studies involving 1,030 cases and 1,683 controls and showed that there was no significant association between G870A polymorphism and HCC risk in the overall populations in the five genetic models. The results

are consistent with most case–control studies.[21,27,29] It seems that G870A polymorphism is not likely to affect HCC risk. However, after being stratified by ethnicity, G870A polymorphism presented as a risk factor for HCC in Caucasian populations but not among Asians in any of the five genetic models. These results were consistent with a related study by Chen et al,[23] which suggested that G870A polymorphism may be associated with the risk of digestive tract cancers, specifically among Caucasians. The reason may be that the environment they lived in and the genetic backgrounds influence the relationship between G870A polymorphism and HCC risk. Moreover, the same polymorphisms playing different roles in tumor susceptibility among different ethnic populations have been detected in numerous studies in recent years.[32–34]

To the best of our knowledge, the findings of this meta-analysis provide more comprehensive and detailed analysis of whether G870A polymorphism is correlated with HCC risk. Nevertheless, the results are limited by the designs of the included studies. First, the controls in the included studies were not uniformly defined, such that it was impossible to determine which controls were population based and which were hospital based. Second, the P-value of HWE was <0.05 in the study by Elkhashab et al,[28] suggesting that this study population was not representative of the broader target population. Nevertheless, we decided to retain this study in the meta-analysis because excluding it did not significantly affect the pooled ORs (data not shown). Third, HCC risk may also depend on numerous confounding factors that we did not account for in the meta-analysis, such as HBV status, tumor status, sex, and age. We could not adjust for these factors using subgroup analyses because most studies either did not report these baseline data or aggregated them in different ways. Fourth, methods used to test for polymorphisms were not uniform and they varied in sensitivity and specificity, which may reduce the robustness of the meta-analysis. Finally, this meta-analysis included only two studies from Caucasian populations and none from African; larger, well-designed studies in Caucasian and African populations are warranted to reevaluate these associations.

Conclusion

Available evidence suggests that no significant association between G870A polymorphism and HCC risk was found in either total populations or Asian populations. However, significant association was found in Caucasian populations. These results should be verified and extended in further detailed and well-designed studies involving larger, multi-ethnic samples.

Disclosure

The authors report no conflicts of interest in this work.

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