CCND1 G870A polymorphism and colorectal cancer risk: An updated meta-analysis

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Abstract. Molecular epidemiological studies have revealed a closer association between cyclin D1 (CCND1) polymorphism and the risk of colorectal cancer; however, the results were inconsistent. The aim of the present meta-analysis was to investigate the association between CCND1 G870A polymorphism and colorectal cancer risk. Online electronic databases (PubMed and Embase) were searched. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association between CCND1 G870A polymorphism and the risk of colorectal cancer. In addition, heterogeneity, publication bias and sensitivity analysis were performed to guarantee the statistical power. In total, 23 published case-control studies with 6,320 patients and 8,252 controls were selected. Significantly increased risks were observed in four genetic models (A vs. G: OR=1.09, 95% CI=1.00-1.18, I^2=54.3%; GA vs. GG: OR=1.13, 95% CI=1.04-1.24, I^2=18.2%; AA vs. GG, OR=1.17: 95% CI=1.00-1.38, I^2=52.5%; GA+AA vs. GG: OR=1.14, 95% CI=1.05-1.24, I^2=33.8%). Similarly, significant associations were also identified in the stratified analysis in the cancer subtype of sporadic colorectal cancer (GA vs. GG: OR=1.21, 95% CI=1.04-1.42, I^2=24.1%; GA+AA vs. GG: OR=1.18, 95% CI=1.02-1.37, I^2=35.0%), Caucasian population (GA vs. GG, OR=1.14, 95% CI=1.02-1.28, I^2=19.8%; GA+AA vs. GG, OR=1.14, 95% CI=1.02-1.27, I^2=37.5%) and other subgroups of control design and genotyping type. The present updated meta-analysis suggested that CCND1 G870A may present an increased risk for developing colorectal cancer, particularly in sporadic colorectal cancer and a Caucasian population.

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Introduction

Colorectal cancer is one of the most common malignant diseases. In 2009, there were 146,970 new patients and 49,920 mortalities in the United States, with colorectal cancer ranking third overall in terms of incidence and mortality in men and women (1). Colorectal cancer is a multifactorial disease, resulting from complex interactions between environmental factors and genetic mutations. A number of studies have revealed that diet may be involved in the development of colorectal cancer (2,3). The abnormal intake of animal meat, fat, vegetables and vitamins may increase the risk of development of colorectal cancer. In addition, family history and genetic factors are also closely associated with colorectal cancer; for example, MutS homolog 2 (MSH2) and MutL homolog 1 (MLH1) gene mutations are associated with hereditary non-polyposis colorectal cancer (3).

Aberrant cellular proliferation is closely associated with the development of cancers. The cyclin family is considered to exert a key role in cell proliferation. Cyclin D1 (CCND1) is a major regulator protein, which fulfills a critical role during transition from the growth (G)1 to the synthesis (S) phase, promoting the progression of the cell cycle during cell mitosis by adhering to cyclin-dependent kinases (CDKs) 4 and 6 (4,5). The constitutively increased expression of CCND1 is observed in numerous malignant cancers, and is associated with a poor prognosis (6-8).

Single nucleotide polymorphisms (SNPs) are able to change the structure of the genome and influence protein expression and function, which leads to abnormal cell proliferation and an increased risk of cancer (9). The most common mutation locus of the CCND1 gene is at codon 242, with a nucleotide change from guanine (G) to adenine (A) in exon 4. The A allele increases the frequency of alternative splicing during cell transcription, leading to an elevated level of CCND1, and consequently resulting in abnormal cell proliferation and an escape from apoptosis (10).

In 2009, Kong *et al* (11) reported the first case-control study on the CCND1 G870A polymorphism and colorectal cancer risk, but no significant differences in genotyping were observed in a population in the United States. To date, several molecular epidemiological investigations have been performed to evaluate the association between the CCND1 G870A polymorphism and colorectal cancer susceptibility, although the results were inconsistent. In the present investigation, a meta-analysis of published case-control studies was therefore performed to precisely assess the association between the CCND1 G870A polymorphism and the risk of colorectal cancer.

Materials and methods

This meta-analysis was designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Compliant) statement (12).

Search strategy. A comprehensive online search of the PubMed and Embase databases was performed for studies published up to June 1 2015 using the following search terms: 'CCND1', 'cyclin D1', 'colorectal cancer', 'colon cancer', 'rectum cancer' and 'polymorphism'. Additional studies were searched for from the references of the retrieved studies, or from review articles on this topic. The following criteria were used to include identified studies in this meta-analysis: (i) a case-control study of the CCND1 G870A polymorphism and colorectal cancer risk; and (ii) sufficient data for estimating odds ratios (ORs) with 95% confidence intervals (CIs). In cases of partly or completely overlapping data, only the latest study, or the study with the larger sample, was included (13,14).

Data extraction. The following data were extracted from all selected studies independently by two investigators (Xiao-Ming Xu and Xiao-Bing Ni): the first author's name, publication data, country origin, racial descent of the study population (Asian, Caucasian or mixed), sources of the controls, genotype distribution, genotyping methods, adherence to the Hardy-Weinberg equilibrium (HWE), minor allele frequency (MAF) in controls, and tumor subtypes.

Statistical analysis. Five genotype models were evaluated based on ORs and 95% CIs to assess the potential association between CCND1 G870A polymorphisms and the risk of colorectal cancer: An allele contrast model (A vs. G), a pair of co-dominant models (AA vs. GG and GA vs. GG), a dominant model (GA+AA vs. GG) and a recessive model (AA vs. GG+GA). Subgroup analyses were performed according to ethnicity and control design. The study heterogeneity was assessed using Cochran's Q statistic and the I^2 statistic (15). ORs were pooled using a random effects model with the inverse variance (I-V) method (or the DerSimonian and Laird method) when statistical heterogeneity was identified to exist (P<0.10 or I^2>50%) (16); otherwise, a fixed effects model (the Mantel-Haenszel method) was adopted (17).

Funnel plots and Egger's linear regression method were used to assess any possible publication bias (18). Cumulative meta-analyses were also performed to identify possible trends in the pooled estimate according to the publication year (19).

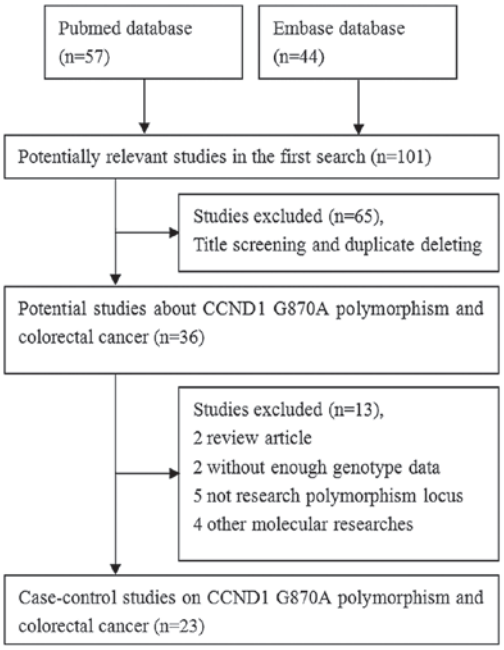

Figure 1. Flow diagram of the study selection process. CCND1, cyclin D1.

All statistical analyses were performed using Stata® version 11.0 (Stata Corporation, College Station, TX, USA). A two-sided P<0.05 was considered to indicate a statistically significant value.

Results

Study characteristics. A total of 101 associated studies were searched. During the first step, while screening the title and screening for duplicates, 65 studies were excluded. Of the remaining 36 articles, 13 were excluded since two were reviews, two did not include sufficient genotype data, five were not focused on the polymorphism locus, and four were on other molecular studies. The flow chart of study selection is shown in Fig. 1. Ultimately, 23 published case-control studies met the inclusion criteria, including 6,320 patients with colorectal cancer and 8,352 controls (11,20-41). The genotype distribution in each study is shown in Table I. The diverse genotyping methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), PCR-single strand conformation polymorphism, PCR Sequenase™ and TaqMan®. Overall, the MAF in controls ranged between 0.412 and 0.614 in Caucasians, and between 0.182 and 0.634 in Asians. In only one study did the control population significantly deviate from the HWE (29).

Meta-analysis. The evaluation of the association between CCND1 G870A polymorphisms and colorectal cancer risk is shown in Table II. Overall, four of the genetic models revealed that the CCND1 G870A polymorphism was significantly associated with an increased risk of colorectal cancer (A vs. G, OR=1.09, 95% CI=1.00-1.18, I^2=54.3%; GA vs. GG, OR=1.13, 95% CI=1.04-1.24, I^2=18.2%; AA vs. GG, OR=1.17, 95% CI=1.00-1.38, I^2=52.5%; and GA+AA vs. GG, OR=1.14, 95% CI=1.05-1.24, I^2=33.8%; Fig. 2). Similarly, significant risk effects were detected in the

Table I. Characteristics of case-control studies included in the present meta-analysis.

Authors	Year	Country/ region	Racial descent	Source of controls	Case	Control	Genotype distribution						Genotyping type	P-value for HWE[a]	MAF	Type	Refs.
							Case			Control							
							GG	GA	AA	GG	GA	AA					
Kong *et al*	2000	USA	Caucasian	Family-control	49	37	9	36	4	10	21	6	PCR-SSCP	0.366	0.446	HNPCC	(11)
McKay *et al*	2000	UK	Caucasian	Population-control	100	101	25	58	17	34	50	17	PCR-RFLP	0.849	0.416	sCRC	(20)
Kong *et al*	2001	USA	Caucasian	Healthy control	156	152	36	71	49	45	84	23	PCR-SSCP	0.112	0.428	sCRC	(21)
Bala *et al*	2001	Finland	Caucasian	Family-control	146	186	50	70	26	47	97	42	PCR-SSCP	0.551	0.487	HNPCC	(22)
Porter *et al*	2002	UK	Caucasian	Hospital-control	334	171	85	175	74	60	81	30	PCR-RFLP	0.768	0.412	CRC	(23)
			Caucasian	Hospital-control	99	171	30	47	22	60	81	30	PCR-RFLP	0.768	0.412	HNPCC	
			Caucasian	Hospital-control	128	171	34	65	29	60	81	30	PCR-RFLP	0.768	0.412	sCRC	
Le Marchand *et al*	2003	USA	Mixed	Population-control	504	624	109	253	142	164	315	145	PCR-RFLP	0.792	0.485	CRC	(24)
			Caucasian	Population-control	208	244	34	110	64	68	120	56	PCR-RFLP	0.792	0.475	CRC	
			Asian	Population-control	296	380	75	143	78	96	195	89	PCR-RFLP	0.792	0.491	CRC	
Grieu *et al*	2003	Australia	Caucasian	Hospital-control	569	327	142	313	114	90	158	79	PCR-SSCP	0.556	0.483	sCRC	(25)
Hong *et al*	2005	Singapore	Asian	Healthy control	254	101	55	128	71	12	50	39	PCR-RFLP	0.505	0.634	sCRC	(26)
Jiang *et al*	2006	India	Asian	Healthy control	301	291	46	130	125	56	145	90	PCR-RFLP	0.860	0.558	CRC	(27)
Schernhammer *et al*	2006	USA	Caucasian	Population-control	610	1,237	125	311	174	264	593	380	TaqMan®	0.250	0.614	CRC	(28)
Huang *et al*	2006	China	Asian	Hospital-control	831	1,052	126	411	294	199	464	389	PCR-RFLP	0.004	0.590	sCRC	(29)
Probst-Hensch *et al*	2006	Singapore	Asian	Population-control	300	1,169	56	132	112	207	548	414	TaqMan®	0.272	0.589	CRC	(30)
Krüger *et al*	2006	Germany	Caucasian	Population-control	406	245	141	188	77	73	121	51	PCR Sequenase™	0.947	0.455	HNPCC	(31)
Grünhage *et al*	2008	Germany	Caucasian	Hospital-control	194	218	37	93	64	48	109	61	PCR-RFLP	0.958	0.530	CRC	(32)
			Caucasian	Hospital-control	98	218	13	50	35	48	109	61	PCR-RFLP	0.958	0.530	HNPCC	
			Caucasian	Hospital-control	96	218	24	43	29	48	109	61	PCR-RFLP	0.958	0.530	sCRC	
Tan *et al*	2008	Germany	Caucasian	Population-control	498	600	120	263	115	147	310	143	PCR-RFLP	0.414	0.497	CRC	(33)
Forones *et al*	2008	Brazil	Mixed	Hospital-control	123	120	36	66	21	34	67	19	PCR-RFLP	0.141	0.438	CRC	(34)
Talseth *et al*	2008	Australia	Caucasian	Hospital-control	157	153	34	78	45	42	80	31	TaqMan®	0.527	0.464	HNPCC	(39)
Liu *et al*	2010	China	Asian	Population-control	373	838	66	187	120	160	429	249	PCR-RFLP	0.303	0.553	CRC	(35)
Kanaan *et al*	2010	USA	Caucasian	Hospital-control	75	93	19	39	17	24	48	21	TaqMan®	0.748	0.484	sCRC	(36)
Yaylim-Eraltan *et al*	2010	Turkey	Caucasian	Hospital-control	57	117	9	28	20	29	60	28	PCR-RFLP	0.781	0.496	CRC	(37)
Jelonek *et al*	2010	Poland	Caucasian	Population-control	50	153	12	33	5	44	71	38	PCR-RFLP	0.383	0.480	CRC	(38)
Sameer *et al*	2013	India	Asian	Healthy control	130	160	19	70	41	41	76	43	PCR-RFLP	0.528	0.506	CRC	(40)
Govatati *et al*	2014	India	Asian	Healthy control	102	107	54	39	10	71	33	3	TaqMan®	0.719	0.182	CRC	(41)

[a]HWE, Hardy-Weinberg equilibrium in control; MAF, minor allele frequency in controls; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction-single strand conformation polymorphism; CRC, colorectal cancer; HNPCC, hereditary non-polyposis colorectal cancer; sCRC, sporadic colorectal cancer.

Table II. Summary of the ORs and 95% CIs of the CCND1 G870A polymorphism and colorectal cancer risk.

		A vs. G				GA vs. GG				AA vs. GG				GA+AA vs. GG				AA vs. GG+GA			
Parameter	N[a]	OR	95% CI	P-value	I^2	OR	95% CI	P-value	I^2	OR	95% CI	P-value	I^2	OR	95% CI	P-value	I^2	OR	95% CI	P-value	I^2
Total	23	1.09	1.00-1.18	<0.01	54.3	1.13	1.04-1.24	<0.01	18.2	1.17	1.00-1.38	0.05	52.5	1.14	1.05-1.24	<0.01	33.8	1.08	0.95-1.23	0.23	54.7
HWE-yes	22	1.09	1.00-1.19	0.05	56.3	1.10	1.01-1.21	0.04	12.8	1.17	0.99-1.40	0.07	54.6	1.12	1.03-1.22	<0.01	34.2	1.10	0.95-1.26	0.20	55.1
Subtype																					
HNPCC	6	1.06	0.86-1.31	0.59	59.5	0.98	0.79-1.22	0.88	37.3	1.13	0.72-1.76	0.60	58.9	1.08	0.78-1.51	0.63	54.8	1.08	0.87-1.35	0.48	37.1
sCRC	8	1.06	0.91-1.24	0.46	59.0	1.21	1.04-1.42	0.02	24.1	1.13	0.82-1.56	0.45	59.9	1.18	1.02-1.37	0.03	35.0	1.04	0.80-1.35	0.77	62.2
Ethnicity																					
Caucasian	15	1.09	0.98-1.22	0.10	56.1	1.14	1.02-1.28	0.02	19.8	1.19	0.95-1.90	0.13	56.7	1.14	1.02-1.27	0.02	37.5	1.08	0.89-1.30	0.43	57.2
Asian	8	1.10	0.96-1.26	0.16	64.2	1.12	0.91-1.37	0.30	48.3	1.20	0.95-1.27	0.18	60.3	1.16	0.94-1.43	0.17	55.2	1.11	0.92-1.34	0.28	57.2
Mixed	1	1.01	0.70-1.44	0.97	NA	0.93	0.52-1.66	0.81	NA	1.04	0.48-2.27	0.91	NA	0.96	0.55-1.67	0.87	NA	1.09	0.56-2.16	0.79	NA
Design																					
Fam-B	2	0.80	0.61-1.06	0.12	0	1.02	0.38-2.75	0.97	66.9	0.60	0.34-1.08	0.09	0	0.92	0.38-2.23	0.86	616	0.69	0.42-1.15	0.16	0
Heal-B	5	1.27	0.92-1.75	0.14	79.5	1.16	0.81-1.68	0.42	50.3	1.64	0.82-3.27	0.16	78.7	1.30	0.86-1.96	0.22	653	1.47	0.88-2.47	0.15	78.2
Hosp-B	8	1.10	1.01-1.19	0.03	13.6	1.29	1.10-1.50	<0.01	0	1.24	1.05-1.48	<0.01	4.7	1.27	1.10-1.46	<0.01	0	1.03	0.90-1.17	0.69	33.3
Pop-B	8	1.03	0.96-1.19	0.43	17.5	1.06	0.94-1.20	0.32	0.6	1.05	0.92-1.21	0.46	18.7	1.06	0.95-1.19	0.30	0	1.02	0.81-1.13	0.77	33.5
Genotyping type																					
PCR-RFLP	13	1.10	1.04-1.18	<0.01	48.7	1.21	1.08-1.36	<0.01	13.0	1.24	1.09-1.41	<0.01	45.5	1.22	1.09-1.36	<0.01	25.1	1.08	0.98-1.19	0.11	49.2
PCR-SSCP	4	1.04	0.76-1.41	0.81	73.1	1.08	0.85-1.37	0.53	42.7	1.05	0.54-2.05	0.87	74.1	1.07	0.75-1.54	0.71	51.4	0.99	0.52-1.91	0.98	80.5
Taqman	5	1.11	0.94-1.32	0.22	54.1	1.09	0.91-1.30	0.36	0	1.09	0.89-1.33	0.42	45.9	1.10	0.93-1.30	0.27	14.9	1.04	0.89-1.21	0.65	49.5
Others	1	0.87	0.70-1.09	0.23	NA	0.80	0.56-1.16	0.24	NA	0.78	0.50-1.23	0.28	NA	0.80	0.57-1.12	0.20	NA	0.89	0.60-1.32	0.57	NA

[a]Numbers of comparisons. NA, not available; HNPCC, hereditary non-polyposis colorectal cancer; sCRC, sporadic colorectal cancer; Fam-B, family-based; Heal-B, healthy-based; Hosp-B, hospital controls; Pop-B, population controls; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction-single strand conformation polymorphism.

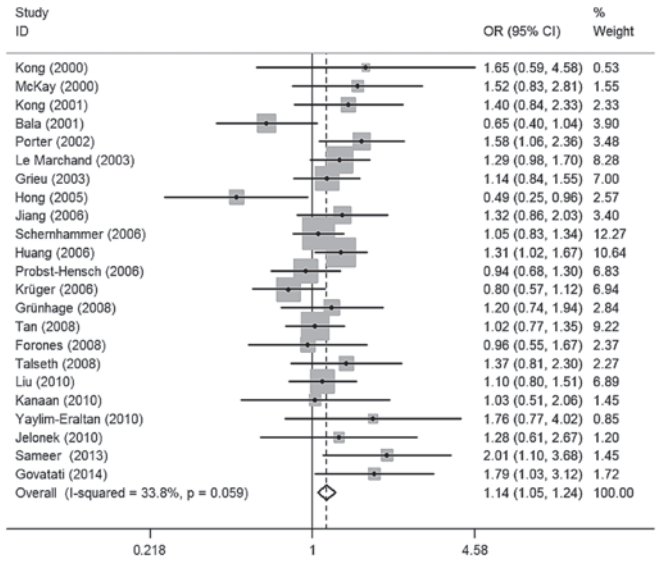

Figure 2. ORs and 95 % CIs for the association between the CCND1 G870A polymorphism and colorectal cancer risk in the GA+AA vs. GG model. CCND1, cyclin D1; OR, odds ratio; CI, confidence interval.

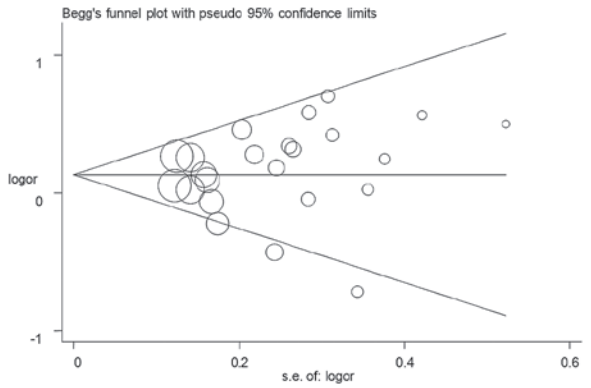

Figure 3. Funnel plot analysis to detect publication bias for the GA+AA vs. GG model of the CCND1 G870A polymorphism and colorectal cancer risk. or, odds ratio; s.e., standard error; CCND1, cyclin D1.

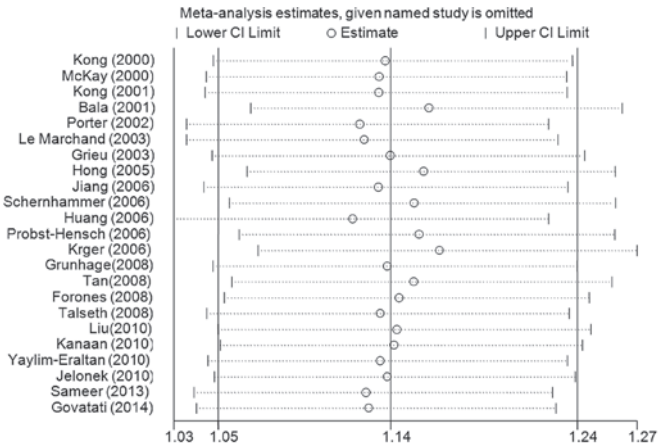

Figure 4. Sensitivity analysis through deleting each study to reflect the influence of the individual data-set to the pooled ORs in the GA+AA vs. GG model of the CCND1 G870A polymorphism and colorectal cancer risk. OR, odds ratio; CI, confidence interval; CCND1, cyclin D1.

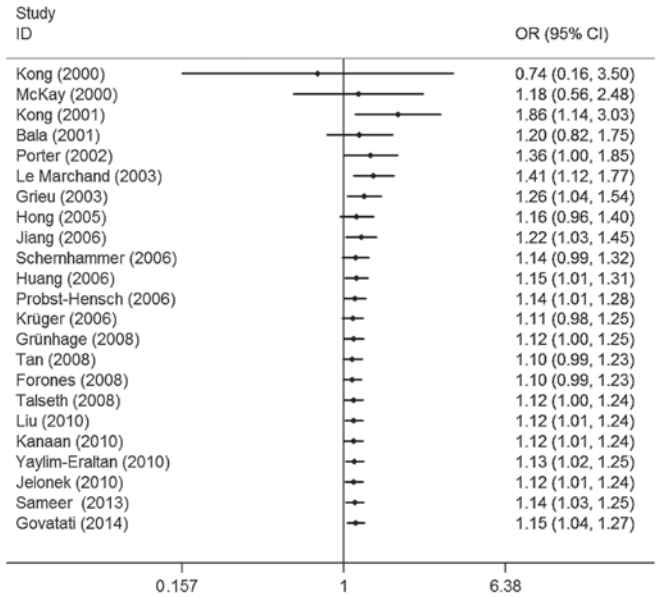

Figure 5. Cumulative meta-analyses according to publication year in the GA+AA vs. GG model of the CCND1 G870A polymorphism and colorectal cancer risk. OR, odds ratio; CI, confidence interval; CCND1, cyclin D1.

subgroup analysis of patients with sporadic colorectal cancer (GA vs. GG, OR=1.21, 95% CI=1.04-1.42, I^2=24.1%; GA+AA vs. GG, OR=1.18, 95% CI=1.02-1.37, I^2=35.0%) and Caucasians (GA vs. GG, OR=1.14, 95% CI=1.02-1.28, I^2=19.8%; GA+AA vs. GG, OR=1.14, 95% CI=1.02-1.27, I^2=37.5%). Significantly increased risks were also detected in the stratified analysis of hospital-based studies and studies employing the PCR-PRFLP genotyping method (Table II).

Publication bias. No publication bias was detected in any of the five genetic models. The shape of the funnel plots appeared to be symmetrical for all models (the GA+AA vs. GG model is shown in Fig. 3), and Egger's test results supported these findings (for A vs. G: P=0.34; for GA vs. GG: P=0.67; for AA vs. GG: P=0.53; for AA+GA vs. GG: P=0.47; and for AA vs. GG+GA: P=0.49).

Sensitivity analysis and cumulative analysis. Sensitivity analyses were performed, and the exclusion of no single study qualitatively changed the pooled ORs, indicating that the results of the present meta-analysis were stable (the data for the GA+AA vs. GG model is shown in Fig. 4). Cumulative analyses according to the publication date revealed that the cancer risk increased gradually, and became positive, on inclusion of the study conducted by Talseth *et al* (39) in 2008 (the GA+AA vs. GG model is shown in Fig. 5).

Discussion

CCND1 is located on chromosome 11q13, and encodes a critical cell cycle regulatory protein of 295 amino acids. CCND1 regulates the transition from the G1 to the S phase during cell division. High levels of activity of CCND1 result in premature cell passage through the G1-S transition, leading to an extension of non-repaired DNA damage and the accumulation of genetic mistakes (42). Overexpression of CCND1 has been

detected in several cancer types, which is also regarded as a risk factor for cancer development. Of the SNPs in CCND1, the G-to-A mutation is the most common, and does not result in an amino acid alteration in the protein sequence. However, the A allele change does lead to an alternatively spliced transcript of CCND1, with a longer half-life compared with the G allele, which facilitates the passage of the variant cell through the G1-S checkpoint and rapid proliferation, ultimately resulting in cancer development (43). Previous studies have shown that the A allele may be associated with an increased risk of breast, prostate, esophageal and other cancer types in different ethnicities (44-46).

In 2000, the first case-control study performed by McKay *et al* (20) failed to reveal any significant association between the CCND1 G870A polymorphism and the risk of colorectal cancer in Caucasians. To date, conflicting data about the association between the CCND1 G870A polymorphism and colorectal cancer susceptibility exist. Kong *et al* (21) identified that the risk of developing colorectal cancer was 3-fold higher in Caucasians with a homozygous A allele (OR=2.68, 95% CI=1.38-5.19). The study by Jiang *et al* (27) suggested that the AA genotype may increase the colorectal cancer risk compared with the GG+AG genotype (OR=1.56, 95% CI=1.10-2.21) in an Indian population. Huang *et al* (29) also identified a significant association between the CCND1 G870A polymorphism and the risk of colorectal cancer in young Chinese patients. Notably, the mechanism of the G870A polymorphism differs according to ethnicity. Porter *et al* (23) demonstrated an increased risk of familiar colorectal cancer of almost 2-fold (for GA+AA vs. GG: OR=1.7, 95% CI=1.1-2.7) although the authors did not find any significant association with sporadic colorectal cancer in Caucasians. Le Marchand *et al* (24) reported a significantly increased risk in Hawaiian individuals with a heterozygous GA genotype (OR=3.9, 95% CI=1.2-13.2), and a marginal risk in Caucasians with a homozygous AA genotype (OR=2.1, 95% CI=1.0-4.3), although the authors did not find any significant association in a Japanese population. However, the studies by Bala, Schernhammer, Krüger and other research groups (22,25,28,31,33-36) failed to identify any significant association between the CCND1 G870A polymorphism and colorectal cancer. By contrast, several studies revealed that the A allele exerts a protective function in the development of colorectal cancer (26,30,37,38). The present meta-analysis, comprising 23 case control studies with 6,320 patients with colorectal cancer and 8,252 controls, explored the association between an increased risk of colorectal cancer and the CCND1 G870A polymorphism. The findings suggested that CCND1 exerts an important role in the development of colorectal cancer, particularly in Caucasians and in the development of sporadic colorectal cancer.

Several limitations of the present analysis should be acknowledged. First, the results are based on the unadjusted estimates, without the original data from the selected studies, and lack information on certain co-variables, including diet, smoking, drinking and other environmental factors. Secondly, small numbers of patients were included in the cancer subgroups, including cancer location and familiar hereditary, which prevented more precise conclusions from being drawn. The actual association could therefore be biased, and the analysis may not have enough statistical power with the current small sample size. Thirdly, the controls in several of the studies were hospital-based populations with other diseases, which could also result in a certain selection bias. Finally, the majority of the included studies were performed in Caucasian and Asian populations, without any reported studies in African populations; therefore, ethnicity may also result in a certain bias. Despite these limitations, the present meta-analysis included 23 published articles with the largest sample sizes and latest data. A cumulative analysis also demonstrated that the results of our meta-analysis were stable, which further confirm the reliability and validity of the present study.

In conclusion, the present meta-analysis suggested that the CCND1 G870A polymorphism may be associated with an increased risk of the development of colorectal cancer. Considering the limitations due to the small sample size, larger, well-designed case-control studies are required to further validate these findings.

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