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The association between CCND1 G870A polymorphism and colorectal cancer risk A meta-analysis

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Abstract

Background: CyclinD1 (CCND1) is a key cell cycle regulatory protein. A large number of epidemiological studies have assessed the potential correlation between the CCND1 G870A polymorphism and the risk of colorectal cancer (CRC), but their findings have been inconsistent. To obtain a more precise understanding of the association between the G870A polymorphism in the CCND1 gene and the CRC risk, we conducted a more comprehensive meta-analysis.

Methodology: We searched PubMed, Ovid, Springer, Weipu, China National Knowledge Infrastructure (CNKI), and Wanfang databases, covering all publications (the last search was updated on January 10, 2017). The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were derived from a fixed effect or random effect model. Statistical analyses were performed using Review Manager 5.3 and STATA 10.0 software.

Results: A total of 7276 CRC patients and 9667 controls from 27 publications were included in this meta-analysis. We found that compared with GG homozygote genetic model, AA, AG, AA+AG genetic models of the CCND1 G870A polymorphism were significantly associated with overall CRC risk (AA homozygote genetic model: OR = 1.28, 95% CI = 1.10-1.49; AG heterozygote genetic model: OR = 1.15, 95% CI = 1.06-1.25; AA homozygote + AG heterozygote genetic model: OR = 1.19, 95% CI = 1.07-1.33). Subgroup analyses by ethnicity and cancer location showed that A carriers were consistently associated with a significantly increased risk of CRC in all subsets of participants (Asian and Caucasian; colon cancer and rectal cancer). When stratified by study design, we found a significant association in hospital-based studies (HB), but no significant associations were found in either population-based studies (PB) or family-based studies (FB). According to subgroup analysis by cancer type, the risk of sporadic colorectal cancer (sCRC) and hereditary nonpolyposis colorectal cancer (HNPCC) were not correlated with the CCND1 G870A polymorphism, except AG (AG vs GG: OR = 1.30, 95% CI = 1.11-1.53).

Conclusions: This meta-analysis suggests that the CCND1 G870A polymorphism is associated with an increased risk of CRC, especially that A carriers may be a major risk factor for CRC.

Abbreviations: CCND1 = cyclinD1, Cls = confidence intervals, CNKI = china national knowledge infrastructure, CRC = colorectal cancer, FB = family-based studies, HB = hospital-based studies, HNPCC = hereditary nonpolyposis colorectal cancer, HPLC = high-performance liquid chromatography, HWE = Hardy–Weinberg equilibrium, LMR = lymphocyte-to-monocyte ratio, ORs = odds ratios, PB = population-based studies, PCR = polymerase chain reaction, PCR-RFLP = PCR restriction fragment length polymorphism, PCR-SSCP = single-stranded conformation polymorphism, sCRC = sporadic colorectal cancer.

Keywords: colorectal cancer, cyclinD1 G870A, meta-analysis, polymorphism

1. Introduction

Colorectal cancer (CRC) is a common malignant tumor of the digestive tract, which has become a serious threat to human

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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health. Globally, there were an estimated 1.36 million new cases of CRC and 694,000 deaths in 2012.^[1] The global number of CRC cases is expected to increase by 60% to more than 2.2 million new cases and approximately 1.1 million deaths annually by 2030.^[2] Although effective therapeutic strategies have been developed over the past decades, the 5-year overall survival of CRC still remains unsatisfactory because of the presence of poor prognostic factors such as vascular and neural invasion, a low lymphocyte-to-monocyte ratio (LMR), and tumor stage III/IV.^[1] The economic burden of CRC is substantial. Particularly, the long-term cost of CRC causes huge social burden.^[3] Welch and Robertson^[4] provided evidence that population aged 50 years or older had a steady decline in colorectal cancer. However, according to the same data source, the incidence had steadily increased among people younger than 50 years.^[5] Therefore, it is extremely important to find the risk factors that can lead to CRC except for advanced age. Factors including environment, life style, diet habit, and others all contribute to the development of CRC.^[6,7] Several environmental factors have attributed to the incidence of CRC is more than 85%,^[8] especially smoking, drinking, meat consumption, exposure to aryl amines, and heterocyclic amines.^[9] Approximately 20% of CRC patients have a family history of cancer,

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indicating that genetic factors may play a role in CRC susceptibility.^[10-12] And the discovery is also evidence supporting that the disease has polygenic and multiple-factorial bases.^[13]

Cancer is a genetic and cell-cycle disease, its occurrence and development involve a multistep and polygenic process.^[14] CyclinD1 (CCND1) is a key cell cycle regulatory protein, and its expression and cellular localization is often transformed in human tumor cells. CCND1 is the gate keeping protein that charges regulating the transition through the restriction point in the G1 phase to S phase of the cell cycle. So the mechanisms of CCND1 gene amplification, posttranscriptional or posttranslational modifications, rearrangements, and variant polymorphisms can lead to abnormal protein levels and result in risk of cancer.^[15–18] The common guanine-to-adenine polymorphism at nucleotide position 870 of the CCND1 gene is known to modulate the frequency of alternate splicing and presumably reduce transcript levels.^[19]

It has been demonstrated in recent studies that high levels of CCND1 protein expression are related to poorer outcomes in patients with CRC.^[20,21] And there were many case-control studies that have evaluated the potential impact of CCND1 (G870A) gene polymorphism on the risk of CRC,^[22,23] and meta-analyses have also been performed to investigate the association between the CCND1 G870A polymorphism and the CRC risk.^[24–27] Notwithstanding, their findings remain inconclusive and controversial. Therefore, we conducted this current meta-analysis to provide more compelling evidence for the relationship between the CRC risk and the CCND1 G870A polymorphism.

2. Materials and methods

2.1. Search strategy

We searched 6 online databases including PubMeb, Ovid, Springer, Weipu, China National Knowledge Infrastructure (CNKI), and Wanfang databases (the last search was updated on January 10, 2017). We used a search strategy of Me-SH terms and keywords: "Colorectal Neoplasms or Colon Neoplasms or Rectal Neoplasms or Colorectal cancer or Colon cancer or Rectal cancer" and "CyclinD1 or CCND1 or CyclinD1 G870A or CCND1 G870A" and "Polymorphism, genetic or Polymorphism." The search was restricted to English and Chinese publications.

2.2. Eligibility criteria

The inclusion criteria of studies in our meta-analysis were as follows: studies that evaluated the impact of the G870A polymorphism in the CCND1 gene on the risk of CRC; studies that used a case-control design; studies with sufficient data (genotype distributions for both patients and controls); and genotype distributions of the control population must be consistent with Hardy–Weinberg equilibrium (HWE). The major exclusion criteria were: no control group was included; genotype frequencies or number were not reported; or reviews, abstracts, and duplicate studies.

2.3. Data extraction

Two reviewers independently and carefully extracted the information from all selected publications. Also they reached a

consensus on all the items. If the 2 authors had a debate about the selected studies, a third author would adjudicate disputes. For each selected study the following items of information were extracted and tabulated: first author, year of publication, original country, ethnicity (Caucasian, Asian, or Mixed), study design (population-or hospital-or family-based study, PB, HB, or FB), type of CRC (hereditary nonpolyposis colorectal cancer (HNPCC), sporadic colorectal cancer (sCRC), or mixed) and location of CRC (colon cancer, rectal cancer, or mixed), genotyping methods (polymerase chain reaction (PCR) single-stranded conformation polymorphism (PCR-SSCP), PCR restriction fragment length polymorphism (PCR-RFLP), high-performance liquid chromatography (HPLC), TaqMan PCR, or Multiplex PCR), as well as the number of patients and controls.

2.4. Statistical analysis

For each study, the genotype distribution was tested in controls, which was based on HWE using an Internet-based program. The association between the CCND1 G870A polymorphism and the risk of CRC was evaluated by crude ORs with 95% CI. We assessed the CRC risk of individuals with genotype AA versus GG, AG versus GG, AA and AG versus GG, A versus G, respectively. We performed all statistical analyses of the metaanalysis by using Review Manager Version 5.3. A P value of less than.05 was considered statistically significant. Heterogeneity was checked by a χ^2 -based Q statistic among the included studies. When the consequence was P > .10 for the Q-test indicating a lack of heterogeneity among studies, the fixed-effects model was used to calculate the pooled OR; otherwise, the pooled OR was calculated by the random effect model. We performed stratified analyses by ethnicity, location of CRC, study design, and type of CRC, so as to evaluate their specific effects on the risk of CRC. The subgroup analysis by ethnicity was classified as Caucasian, Asian, or Mixed (when the participants were difficult to be divided into Asian or Caucasian, the study was termed "Mixed"). The different classification according to location of CRC was: colon cancer, rectal cancer, or mixed (the specific location was not mentioned). The study design was described as HB, PB, or FB. To evaluate the effect of CRC type, the participants were stratified into sCRC, HNPCC, or mixed (included both sCRC and HNPCC, or the specific type was not mentioned).

Moreover, sensitivity analysis was performed to assess the stability of the results, by orderly excluding individual studies. Publication bias was analyzed by Begg funnel plot and Egger test.^[28,29] All statistical analyses were performed using Review Manager 5.3 and STATA 10.0 software.

3. Results

3.1. Study inclusion and characteristics

As shown in Fig. 1, we searched PubMed, Ovid, Springer, CNKI, Wanfang, and Weipu database. Initially, a total of 403 results were identified on CCND1 and CRC. Then 4 articles were excluded as previous meta-analyses. After reading the titles and abstracts, 365 were excluded because they were irrelevant to CCND1 G870A polymorphism and 34 potential articles were included for full-text review. After reading the full texts, 7 articles were excluded to duplicates (n=5), review (n=1), or lack of the relevant date (n=1). Finally, a total of 33 case-control studies from 27 publica-

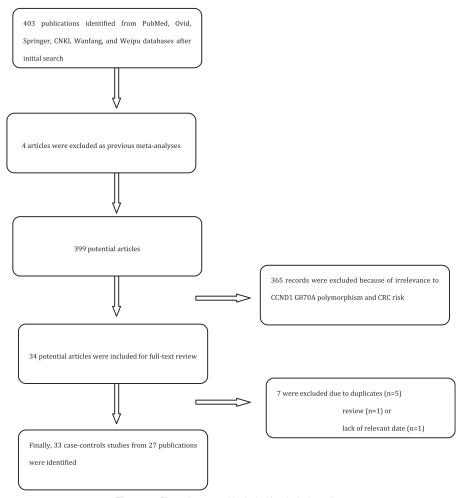


Figure 1. Flow diagram of included/excluded studies.

tions^[14,22,23,30–53] which met our inclusion criteria, including 7276 cases and 9667controls. The main characteristics of each study identified are listed in Table 1. Briefly, 12 case-control studies were performed in Asians, ^[22,23,36–38,40,41,44,45,50,52,53] 12 in Caucasians, ^[14,31–36,39,42,46,47,51] 5 in Mixed. ^[30,36,43,48,49] As for study design, there were 2 FB, ^[30,31] 14 PB, ^[14,23,32,33,36,37,39,41–45,48,50,53] and 11 HB. ^[22,34,35,38,40,43,46,47,49,51,52] Eleven studies described the specific location of CRC. ^[14,22,23,36,38,40,43,48,50,52,53] Genotype and allele distributions for each case-control study are shown in Table 2.

3.2. Main meta-analysis results

The heterogeneity between AA + AG versus GG was assessed for the 33 studies (P=.02) and the χ^2 value was 42.59 with 26 degrees of freedom (Fig. 2). Therefore, a random-effects model was used for the synthesis of data. The overall OR was 1.19 (95% CI=1.07–1.33) and the Z test value for overall effect was 3.31 (P=.0009). The results suggested that the variant A allele carriers had a 19% increased risk of CRC. We also found that compared with GG homozygote, AA homozygote, or AG heterozygote of the CCND1 G870A polymorphism was significantly associated with a higher overall risk for CRC (AA vs GG: OR=1.28, 95% CI=1.10–1.49; AG vs GG: OR=1.15, 95% CI=1.06–1.25). Summary results of other genetic comparisons are listed in Table 3.

3.3. Subgroup analyses

We performed subgroup analyses by ethnicity (Asian or Caucasian), location of CRC (colon cancer or rectal cancer), study design (PB, HB, or FB), and type of CRC (sCRC or HNPCC). Using GG genotype as a reference, A carriers were associated with a significantly increased risk of CRC in both Asians (AA+AG vs GG: OR=1.24, 95% CI=1.04-1.49) and Caucasians (AA+AG vs GG: OR=1.19, 95% CI=1.01-1.40). This indicated that A carriers might be a low-penetrant risk factor for CRC in both Asian and Caucasian populations. When stratified by cancer location, significant associations between A carriers and CRC risk were found in both subsets of patients with colon cancer (AA+AG vs GG: OR=1.20, 95% CI=1.05-1.38) and rectal cancer (AA+AG vs GG: OR=1.39, 95% CI=1.20-1.62). Subgroup analysis by study design indicated that significant association between the CCND1 G870A polymorphism and the risk of CRC was only observed in HB studies (AA +AG vs GG: OR = 1.30, 95% CI = 1.14-1.47), rather than PB (OR = 1.16, 95% CI = 1.00–1.35) or FB studies (OR = 0.92, 95% CI=0.38-2.23). According to analysis by cancer type, no

Table 1

First author	Year	Country	Ethnicity	Study design	Type of cancer	Genotyping method	total (Cases/controls)	Reference
Kong	2000	US	Mixed	FB	HNPCC	PCR-SSCP	86 (49/37)	[30]
McKay	2000	UK	Caucasian	PB	sCRC	PCR-RFLP	201 (100/101)	[31]
Bala	2001	American	Caucasian	FB	HNPCC	Multiplex PCR	332 (146/286)	[32]
Kong	2001	US	Caucasian	PB	Mixed	PCR-SSCP	308 (156/152)	[33]
Porter	2002	UK	Caucasian	PB	Mixed	PCR-RFLP	505 (334/171)	[34]
Porter	2002	UK	Caucasian	PB	HNPCC	PCR-RFLP	270 (99/171)	[34]
Porter	2002	UK	Caucasian	PB	sCRC	PCR-RFLP	299 (128/171)	[34]
Grieu	2003	Australia	Caucasian	HB	sCRC	PCR-SSCP	896 (569/327)	[35]
Lewis	2003	US	Caucasian	HB	sCRC	PCR-RFLP	374 (161/213)	[36]
Le Marchand	2003	US	Mixed	PB	Mixed	PCR-RFLP	1128 (504/624)	[37]
Le Marchand	2003	US	Caucasian	PB	sCRC	PCR-RFLP	299 (138/161)	[37]
Le Marchand	2003	US	Asian	PB	sCRC	PCR-RFLP	676 (296/380)	[37]
Hong	2005	Singapore	Asian	PB	sCRC	PCR-RFLP	355 (254/101)	[38]
Jiang	2006	India	Asian	HB	Mixed	PCR-RFLP	592 (301/291)	[39]
Kruger	2006	Germany	Caucasian	PB	HNPCC	Multiplex PCR	406 (315/245)	[40]
Huang	2006	Taiwan	Asian	HB	sCRC	PCR-RFLP	1883 (831/1052)	[41]
Probst-Hensch	2006	Singapore	Asian	PB	Mixed	TaqMan PCR	1469 (300/1169)	[42]
Schernhammer	2006	US	Caucasian	PB	Mixed	TaqMan PCR	1847 (610/1237)	[43]
Forones	2008	Brazil	Mixed	HB	Mixed	PCR-RFLP	243 (123/120)	[44]
Jing	2008	China	Asian	PB	Mixed	TaqMan PCR	309 (104/205)	[45]
Zhu	2008	China	Asian	PB	Mixed	PCR-RFLP	1015 (345/670)	[46]
Grunhage	2008	Germany	Caucasian	HB	Mixed	PCR-RFLP	412 (194/218)	[47]
Grunhage	2008	Germany	Caucasian	HB	HNPCC	PCR-RFLP	316 (98/218)	[47]
Grunhage	2008	Germany	Caucasian	HB	sCRC	PCR-RFLP	314 (96/218)	[47]
Talseth	2008	Australia/Poland	Caucasian	HB	HNPCC	TaqMan PCR	310 (157/153)	[48]
Tan	2008	Germany	Mixed	PB	Mixed	PCR-RFLP	1098 (498/600)	[49]
Kanaan	2010	US	Mixed	HB	sCRC	PCR-HPLC	168 (75/93)	[50]
Liu	2010	China	Asian	PB	Mixed	PCR-RFLP	1211 (373/838)	[51]
Yaylim-Eraltan	2010	Turkey	Caucasian	HB	Mixed	PCR-RFLP	174 (57/117)	[52]
Sameer	2013	India	Asian	PB	Mixed	PCR-RFLP	290 (130/160)	[53]
Liu	2013	China	Asian	HB	sCRC	PCR-RFLP	243 (125/118)	[54]
Govatati	2014	India	Asian	PB	Mixed	PCR-RFLP	210 (103/107)	[55]
Huang	2015	China	Asian	HB	Mixed	PCR-RFLP	724 (362/362)	[22]

US=United States, UK=United Kingdom, HNPCC=hereditary nonpolyposis colorectal cancer, sCRC=sporadic colorectal cancer, Mixed=it was no mention of the cancer type particularly (HNPCC, no-HNPCC, sCRC, fCRC), FB=family-based study, PB=population-based study, HB=hospital-based study, PCR=polymerase chain reaction, SSCP=single-stranded conformation polymorphism, RFLP=restriction fragment length polymorphism, HPLC=high-performance liquid chromatography.

significant association was noted between the CCND1 G870A polymorphism and an increased risk of CRC in patients with sCRC (AA+AG vs GG: OR=1.24, 95% CI=0.96–1.60) and HNPCC (AA+AG vs GG: OR=0.93, 95% CI=0.64–1.36), but a significantly increased CRC risk was found in sCRC patients with genotype AG (AG vs GG: OR=1.30, 95% CI=1.11–1.53) (Fig. 3, Table 3).

3.4. Sensitivity analysis and publication bias

We performed a sensitivity analysis through sequentially excluded individual studies. No individual study affected the overall OR dominantly, statistically similar results were obtained, suggesting the stability of this meta-analysis (data not shown). We used the Begg funnel plot and the Egger test. The shape of the funnel plots of the 27 publications appeared symmetrical for the AA + AG versus GG model (Fig. 4), indicating no evidence of significant publication bias in this meta-analysis. And the Egger test results also supported that there was no evidence of publication bias (P > .05).

4. Discussion

CRC is the third most common cancer in both men and women across the world.^[1] To date, the pathogenesis of CRC has not yet

been fully clarified. Several risk factors such as age, environment, high-fat diet, and heredity have been recognized. In recent years, numerous studies have revealed a direct relationship between the CCND1 gene and tumors, including lymphoma,^[54,55] breast cancer,^[56,57] lung cancer,^[58,59] bladder cancer,^[60,61] and colorectal cancer.^[62,63] It has been demonstrated that the overexpression of CCND1 may collaboratively participate in cancer carcinogenesis.

As we know, CCND1 has been considered to be a cancer gene which could regulate progression from the G1 phase of the cell cycle to the S phase. Cells with the mutant allele accumulate mutations as a result of defective mismatch repair and bypass the G1-S checkpoint of the cell cycle more easily than in cells not carrying the polymorphism.^[30] Variant polymorphisms can result in abnormal protein levels and lead to cancer.^[20] The CCND1 over expression has been reported to occur in 72% of colorectal tumors.^[62] However, results of case-control studies about this genetic polymorphism were inconsistent. A few meta-analyses^[24–27] were also designed to confirm the influence of CCND1 G870A polymorphism on CRC susceptibility. These analyses found that A carriers of the CCND1 G870A polymorphism were significantly associated with an increased risk of CRC. However, their detailed descriptions on ethnicity, cancer location, study design, and family history varied significantly.

Table 2

Distribution of CCND1 G870A genotype and Allele among colorectal cancers and controls.

		Cases (n)			Controls (n)	Case	es (n)	Contro	ols (n)	HWE for control
Author (year)	AA	AG	GG	AA	AG	GG	Α	G	Α	G	Р
Kong (2000)	4	36	9	6	21	10	44	54	33	41	.37
McKay (2000)	17	58	25	17	50	34	92	108	84	118	.85
Bala (2001)	26	70	50	42	97	47	122	170	181	191	.55
Kong (2001)	49	71	36	23	84	45	169	143	130	174	.11
Porter (2002)	74	175	85	30	81	60	323	345	141	201	.77
Lewis (2003)	26	84	51	31	98	84	136	186	160	266	.78
Grieu (2003)	114	313	142	79	158	90	541	597	316	338	.56
Le Marchand (2003)	142	253	109	145	315	164	537	471	605	643	.79
Hong (2005)	71	128	55	39	50	12	270	238	128	74	.51
Jiang (2006)	125	130	46	90	145	56	380	222	325	257	.86
Kruger (2006)	61	144	110	51	121	73	266	364	223	267	.95
Huang (2006)	294	411	126	389	464	199	999	663	1242	862	.0043
Probst-Hensch (2006)	112	132	56	414	548	207	356	244	1376	962	.27
Schernhammer (2006)	174	311	125	380	593	264	659	561	1353	1121	.25
Forones (2008)	21	66	36	19	67	34	108	138	105	135	.14
Jing (2008)	32	61	11	51	113	41	125	83	215	195	.13
Zhu (2008)	98	186	61	196	351	123	382	308	743	597	.12
Grunhage (2008)	64	93	37	61	109	48	221	167	231	205	.96
Talseth (2008)	45	78	34	31	80	42	168	146	142	164	.53
Tan (2008)	115	263	120	143	310	147	493	503	596	604	.41
Kanaan (2010)	17	39	19	21	48	24	73	77	90	96	.75
Liu (2010)	120	187	66	249	429	160	427	319	927	749	.3
Yaylim-Eraltan (2010)	20	28	9	28	60	29	68	46	116	118	.78
Sameer (2013)	41	70	19	43	76	41	152	108	162	158	.53
Liu (2013)	55	49	21	29	51	38	159	91	109	127	.16
Govatati (2014)	10	39	54	3	33	71	59	147	39	175	.72
Huang (2015)	135	180	47	89	212	61	450	274	390	334	.00069

 $\label{eq:ccnd1} CCND1 \ = \ cyclinD1, \ HWE \ = \ Hardy \ - \ Weinberg \ equilibrium.$

Bala(2001) Forones(2008) Govatati(2014) Grunhage(2008) Hong(2005) Huang(2006) Huang(2015) Jiang(2006) Jiang(2008) Kanaan(2010) Kong(2000)	Events 96 87 49 427 157 199 705 315 255 93 56 40	146 123 103 569 194 254 831 362 301 104 75	139 86 36 237 170 89 853 301 235 164	186 120 107 327 218 101 1052 362 291	3.3% 2.7% 2.6% 5.5% 3.3% 2.0% 6.7% 4.0%	<u>M-H, Random, 95% CI</u> 0.65 (0.40, 1.04) 0.96 (0.55, 1.67) 1.79 (1.03, 3.12) 1.14 (0.84, 1.55) 1.20 (0.74, 1.94) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.36 (0.90, 2.05)	M-H, Random, 95% Cl
Forones(2008) Govatati(2014) Grieu(2003) Grunhage(2008) Hong(2005) Huang(2006) Huang(2015) Jiang(2008) Kanaan(2010) Kong(2000)	87 49 427 157 199 705 315 255 93 56	123 103 569 194 254 831 362 301 104	86 36 237 170 89 853 301 235	120 107 327 218 101 1052 362	2.7% 2.6% 5.5% 3.3% 2.0% 6.7% 4.0%	0.96 [0.55, 1.67] 1.79 [1.03, 3.12] 1.14 [0.84, 1.55] 1.20 [0.74, 1.94] 0.49 [0.25, 0.96] 1.31 [1.02, 1.67]	
Govatati(2014) Grieu(2003) Grunhage(2008) Hong(2005) Huang(2006) Huang(2015) Jiang(2008) Kanaan(2010) Kong(2000)	49 427 157 199 705 315 255 93 56	103 569 194 254 831 362 301 104	36 237 170 89 853 301 235	107 327 218 101 1052 362	2.6% 5.5% 3.3% 2.0% 6.7% 4.0%	1.79 [1.03, 3.12] 1.14 [0.84, 1.55] 1.20 [0.74, 1.94] 0.49 [0.25, 0.96] 1.31 [1.02, 1.67]	
Grieu(2003) Grunhage(2008) Hong(2005) Huang(2006) Huang(2015) Jiang(2006) Jing(2008) Kanaan(2010) Kong(2000)	427 157 199 705 315 255 93 56	569 194 254 831 362 301 104	237 170 89 853 301 235	327 218 101 1052 362	5.5% 3.3% 2.0% 6.7% 4.0%	1.14 [0.84, 1.55] 1.20 [0.74, 1.94] 0.49 [0.25, 0.96] 1.31 [1.02, 1.67]	
Grunhage(2008) Hong(2005) Huang(2006) Huang(2015) Jiang(2006) Jing(2008) Kanaan(2010) Kong(2000)	157 199 705 315 255 93 56	194 254 831 362 301 104	170 89 853 301 235	218 101 1052 362	3.3% 2.0% 6.7% 4.0%	1.20 [0.74, 1.94] 0.49 [0.25, 0.96] 1.31 [1.02, 1.67]	
Hong(2005) Huang(2006) Huang(2015) Jiang(2006) Jing(2008) Kanaan(2010) Kong(2000)	199 705 315 255 93 56	254 831 362 301 104	89 853 301 235	101 1052 362	2.0% 6.7% 4.0%	0.49 [0.25, 0.96] 1.31 [1.02, 1.67]	
Huang(2006) Huang(2015) Jiang(2008) Jing(2008) Kong(2010) Kong(2000)	705 315 255 93 56	831 362 301 104	853 301 235	1052 362	6.7% 4.0%	1.31 [1.02, 1.67]	+
Huang(2015) Jiang(2006) Jing(2008) Kanaan(2010) Kong(2000)	315 255 93 56	362 301 104	301 235	362	4.0%		
Jiang(2006) Jing(2008) Kanaan(2010) Kong(2000)	255 93 56	301 104	235			1.36 [0.90, 2.05]	
Jing(2008) Kanaan(2010) Kong(2000)	93 56	104		291			
Kanaan(2010) Kong(2000)	56		104		3.8%	1.32 [0.86, 2.03]	
Kong(2000)		75		205	1.8%	2.11 [1.04, 4.31]	
	411		69	93	1.9%	1.03 [0.51, 2.06]	
		49	27	37	1.0%	1.65 [0.59, 4.58]	
Kong(2001)	120	156	107	152	3.0%	1.40 [0.84, 2.33]	
Kruger(2006)	205	315	172	245	4.7%	0.79 [0.55, 1.13]	
Le Marchand(2003)	395	504	460	624	6.1%	1.29 [0.98, 1.70]	E.
Lewis(2003)	110	161	129	213	3.8%	1.40 [0.91, 2.16]	
Liu(2010)	307	373	678	838	5.4%	1.10 [0.80, 1.51]	T
Liu(2013)	104	125	80	118	2.3%	2.35 [1.28, 4.32]	
McKay(2000)	75	100	67	101	2.3%	1.52 [0.83, 2.81]	
Porter(2002)	249	334	111	171	4.2%	1.58 [1.06, 2.36]	
Probst-Hensch(2006)	244	300	962	1169	5.2%	0.94 [0.68, 1.30]	-
Sameer(2013)	111	130	119	160	2.3%	2.01 [1.10, 3.68]	
Schernhammer(2006)	485	610	973	1237	6.8%	1.05 [0.83, 1.34]	+
Talseth(2008)	123	157	111	153	2.9%	1.37 [0.81, 2.30]	
Tan(2008)	378	498	453	600	6.1%	1.02 [0.77, 1.35]	+
Yaylim-Eraltan(2010)	48	57	88	117	1.4%	1.76 [0.77, 4.02]	+
Zhu(2008)	284	345	547	670	5.0%	1.05 [0.75, 1.47]	+
Total (95% CI)		7276		9667	100.0%	1.19 [1.07, 1.33]	•
Total events	5717		7463				
Heterogeneity: Tau ² = 0.03		12.59. df		= 0.02);	I ² = 39%		0.01 0.1 1 10 100

Figure 2. Meta-analysis of association between CCND1 G870A polymorphism and colorectal cancer (AA and AG versus GG) when all the subjects in the 27 studies were included (Events: AA+AG; Total: AA+AG+GG). CCND1 = cyclinD1.

Table 3

Association between	CCND1	G870A	polymorphism	and	colorectal cancer.
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Variables		AA versus	GG	AG versus	GG	AA + AG versu	us GG	A versus	G
(no. of studies)		OR and 95% Cl	P value	OR and 95% Cl	P value	OR and 95% CI	P value	OR and 95% Cl	P value
All studies (27)		1.28 (1.10-1.49)	.002	1.15 (1.06–1.25)	.0008	1.19 (1.07–1.33)	.0009	1.13 (1.05–1.23)	.001
Ethnicity	Asian (12)	1.39 (1.08–1.77)	.01	1.16 (1.03–130)	.02	1.24 (1.04-1.49)	.02	1.18 (1.04–1.34)	.01
	Caucasian (12)	1.29 (1.01-1.66)	.04	1.15 (1.06-1.26)	.001	1.19 (1.01-1.40)	.04	1.16 (1.06-1.26)	.0009
Location	Colon cancer (11)	1.30 (1.06–1.58)	.01	1.17 (1.01–1.35)	.03	1.20 (1.05-1.38)	.008	1.15 (1.03–1.29)	.01
	Rectal cancer (11)	1.66 (1.27-2.17)	.0002	1.30 (1.11–1.53)	.001	1.39 (1.20-1.62)	<.0001	1.31 (1.13–1.52)	.0004
Study design	PB (14)	1.22 (0.99-1.51)	.06	1.11 (1.00-1.23)	.05	1.16 (1.00-1.35)	.05	1.10 (1.00-1.22)	.06
	HB (11)	1.70 (1.19–2.45)	.004	1.28 (1.12-1.46)	.0003	1.30 (1.14-1.47)	<.0001	1.22 (1.08-1.38)	.001
	FB (2)	0.60 (0.34-1.08)	.09	0.82 (0.53-1.29)	.4	0.92 (0.38-2.23)	.86	0.80 (0.61-1.06)	.12
Type of cancer	sCRC (10)	1.16 (0.79-1.70)	.45	1.30 (1.11-1.53)	.001	1.24 (0.96-1.60)	.1	1.09 (0.89-1.33)	.39
	HNPCC (6)	0.91 (0.54-1.52)	.71	0.88 (0.68-1.14)	.32	0.93 (0.64-1.36)	.72	0.96 (0.74-1.24)	.75
	Mixed (16)	1.39 (1.16–1.67)	.0005	1.14 (1.03–1.25)	.01	1.43 (1.12–1.81)	.003	1.20 (1.10–1.31)	<.0001

P value for Z test for all studies.

CCND1 = cyclinD1, Cl = confidence interval, FB = family-based study, HB = hospital-based study, HNPCC = nonpolyposis colorectal cancer, Mixed = no mention of the cancer type particularly, OR = odds ratio, PB = population-based study, sCRC = sporadic colorectal cancer.

Zou et al,^[26] the most recent study published in 2012 included 23 case-control studies, and concluded that the CCND1 870A allele might be a low-penetrant risk factor for CRC. The result was consistent with the findings reported by Yang et al^[24] and Zhang et al^[27]. But in further stratified analyses by ethnicity and study design, such a correlation was not found in any subsets of participants. This result was contradictory to those from the other 3 meta-analyses,^[24,25,27] which observed an increased risk in the subgroups of sCRC and in Caucasians.

This meta-analysis of 33 case-control studies supported that the G870A polymorphism of CCND1 was a risk factor for CRC. A allele carriers had a 1.19-fold elevated risk of CRC. As previous studies reported inconsistent findings in their subgroup analyses, we performed more robust stratified analyses to comprehensively analyze these subset associations. Our findings revealed that the CCND1 G870A polymorphism was associated with an increased risk of CRC in both Asian and Caucasian. Meanwhile, such an association was also observed in subsets of either cancer location (colon cancer and rectal cancer). As for the study design, we found a significant association in HB studies, but not in PB or FB studies, which was consistent with a previous meta-analysis.^[24] When stratified by type of CRC, no relationship was identified between the CCND1 G870A polymorphism and the risk of CRC in subsets of patients with either sCRC or HNPCC. We speculated that this might be explained by the differences in case-control conditions, genetic classification method, living environment, genetic background, tumor stage, and/or living habits among the included studies.

It has been shown in prior studies that CCND1 870A allele carriers had been confirmed that may be an increase the risk of developing esophageal cancer and hepatocellular carcinoma.^[64,65] In this study, we come to a similar conclusion that the CCND1 G870A polymorphism is a potential factor of CRC. However, a few meta-analyses^[66,67] reported that the CCND1 G870A polymorphism may not be associated with an increased risk factor for cervical cancer and head and neck cancer. Perhaps this is due to similar CCND1 gene expressions in gastrointestinal carcinomas rather than tumors of other systems.

Compared with previous meta-analyses, we found a significant association between the CCND1 G870A polymorphism and the CRC risk in many different subgroups. We inferred that 3 reasons might explain the different results between our study and prior studies. First, a larger number of case-control studies were included in our meta-analysis than previous studies, so our conclusion seemed to be more powerful and reliable. Second, no conspicuous publication bias was detected in our study, which indicated that the entire pooled results might be unbiased. Third, comparisons of all genetic models were performed in our study, suggesting that this polymorphism analysis might be more comprehensive and credible.

We also acknowledge several limitations of this meta-analysis. First, we only selected articles published electronically in 6 databases, so it is possible that some pertinent studies not included in these databases or unpublished studies with negative results may have been missed. Second, as participants in the control groups were selected from healthy persons or patients, there might be a lack of proper matching of controls in the included studies, which is likely to influence the consistency of our results. Third, only small numbers of participants were included in some subgroups such as subsets of FB studies and HNPCC patients. Therefore, these subgroup analyses may not have enough statistical power with the small sample size and the conclusions may be biased.

In conclusion, this meta-analysis demonstrated that the CCND1 G870A polymorphism may be associated with an increased risk of developing CRC. Subgroup analyses by ethnicity, cancer location, and study design revealed significant associations between the CCND1 G870A polymorphism and CRC susceptibility in A carriers (AA or AG or AA+AG), especially among Asian and Caucasian populations, patients with colon cancer or rectal cancer, and in hospital-based studies. This may provide a vital theoretical basis to understand the effect of the CCND1 G870A polymorphism on the pathogenesis of CRC. As the CCND1 G870A may play an important role in predicting the occurrence and progression of CRC. Our findings may provide valuable insights into the development of novel diagnostic approaches, gene-targeted therapies, and prevention strategies to combat against CRC. Considering the above-mentioned limitations, larger-scale and well-designed studies are still required to further validate these findings and investigate an even wider range of associations in the future.

	Experime Events		Contro Events		Weight M	Odds Ratio I-H. Random, 95% CI	Odds Ratio M-H, Random, 95% Cl	Study or Subgroup	Experin Events		Cont Events		Weight	Odds Ratio M-H, Fixed, 95% C	Odds Ratio M-H, Fixed, 95% Cl
1 Asian							and the set of the second	3.3.1 colon cancer							
vatati(2014)	49	103	36	107	3.1%	1.79 [1.03, 3.12]		Forones(2008)	52	77	86	120	3.2%	0.82 [0.44, 1.53	
na(2005)	199	254	89	101	2.3%	0.49 [0.25, 0.96]		Govatati(2014)	17	38	36		1.5%	1.60 [0.75, 3.40	
ang(2006)	705	831	853	1052	6.9%	1.31 [1.02, 1.67]	+	Huang(2006)	347	412			11.2%	1.25 [0.92, 1.69	
ang(2015)	315	362	301	362	4.5%	1.36 [0.90, 2.05]									· · · · · · · · · · · · · · · · · · ·
ng(2006)	255	301		291	4.3%	1.32 [0.86, 2.03]		Huang(2015)	225	257	301		4.6%	1.42 [0.90, 2.26	
	93	104	164		2.1%	2.11 [1.04, 4.31]		Jiang(2006)	51	59			1.6%	1.52 [0.68, 3.38	
g(2008)							-	Le Marchand(2003)	265	347			11.5%	1.15 [0.85, 1.56	T
Marchand(2003)	221	296		380	5.3%	1.00 [0.70, 1.41]		Liu(2010)	145	178	678	838	6.5%	1.04 [0.68, 1.57	-
(2010)	307	373		838	5.8%	1.10 [0.80, 1.51]		Liu(2013)	39	52	80	118	1.8%	1.43 [0.68, 2.98	
1(2013)	104	125	80	118	2.7%	2.35 [1.28, 4.32]		McKay(2000)	56	76			2.2%	1.42 [0.74, 2.74	
obst-Hensch(2006)	244	300	962		5.6%	0.94 [0.68, 1.30]	T	Sameer(2013)	45	52			1.2%	2.21 (0.93, 5.30	
meer(2013)	111	130	119	160	2.8%	2.01 [1.10, 3.68]									-
u(2008)	284	345	547	670	5.4%	1.05 [0.75, 1.47]	+	Tan(2008)	231	303	453		10.7%	1.04 [0.75, 1.44	
btotal (95% CI)		3524	_	5453	50.9%	1.24 [1.04, 1.49]	•	Subtotal (95% CI)		1851		43/3	56.1%	1.20 [1.05, 1.38]	
al events	2887		4348					Total events	1473		3368				
terogeneity: Tau ² = 0.0		4.03. df=	11 (P=	0.01);	P= 54%			Heterogeneity: Chi ² =	6.55, df =	10 (P=)	0.77); F:	:0%			
st for overall effect Z =								Test for overall effect	Z= 2.65 (P=0.00	8)				
.2 Caucasian								3.3.2 rectal cancer							
	00	4.40	100	100	2.0%	0.0510 40 1.040		Forones(2008)	10	22	00	100	1.10	1 05 10 20 2 02	
la(2001)	96	146	139	186	3.8%	0.65 [0.40, 1.04]			16	22			1.1%	1.05 [0.38, 2.92	
eu(2003)	427	569	237	327	5.9%	1.14 [0.84, 1.55]		Govatati(2014)	32	65			2.0%	1.91 [1.02, 3.59	10
unhage(2008)	157	194	170	218	3.7%	1.20 [0.74, 1.94]	T	Huang(2006)	358	419		1000	10.5%	1.37 [1.00, 1.87	-
ng(2001)	120	156	107	152	3.5%	1.40 [0.84, 2.33]	+	Huang(2015)	90	105	301	362	2.9%	1.22 [0.66, 2.24	
uger(2006)	205	315	172	245	5.2%	0.79 [0.55, 1.13]		Jiang(2006)	204	242			5.0%	1.28 [0.81, 2.01	
Marchand(2003)	109	138	111	161	3.3%	1 69 [1 00, 2 87]		Le Marchand(2003)	124	149			4.4%	1.77 [1.11, 2.82	
wis(2003)	110	161		213	4.3%	1 40 [0.91, 2.16]		and the second se	162	195			6.4%	1.16 10.77, 1.75	
Kay(2000)	75	100	67	101	2.7%	1.52 [0.83, 2.81]		Liu(2010)							
rter(2002)	249	334	111	171	4.6%	1.58 [1.06, 2.36]		Liu(2013)	65	73			1.0%	3.86 [1.68, 8.85	
	485	334 610			4.0%		1	McKay(2000)	19	24			0.8%	1.93 (0.66, 5.61	
hernhammer(2006)			973			1.05 [0.83, 1.34]		Sameer(2013)	66	78	119	160	1.8%	1.89 [0.93, 3.85	
seth(2008)	123	157		153	3.4%	1.37 [0.81, 2.30]		Tan(2008)	147	195	453	600	8.1%	0.99 [0.68, 1.45	+
(lim-Eraltan(2010)	48	57		117	1.7%	1.76 [0.77, 4.02]		Subtotal (95% CI)	2.02	1567			43.9%	1.39 [1.20, 1.62	•
btotal (95% CI)		2937		3281	49.1%	1.19 [1.01, 1.40]		Total events	1283		3368			the lower side	
tal events	2204		2415							10.00		-			
terogeneity: Tau ^a = 0.0	3; Chi ² = 1	8,46, df=	11 (P=	0.07):	P= 40%			Heterogeneity: Chi#=				= 25%			
st for overall effect Z =								Test for overall effect	Z=4.30 (P < 0.00	01)				
tal (95% CI)		6461		8734	100.0%	1.21 [1.08, 1.37]	•	Total (95% CI)		3418		8746	100.0%	1.29 [1.16, 1.43]	
								Total events	2756		6736				
tal cuante	5001														
terogeneity: Tau [#] = 0.0 st for overall effect: Z =	3.22 (P=0	.001)				0.01	0.1 1 10 100 avours [experimental] Favours [control]	Heterogeneity: Chi ² = Test for overall effect. Test for suboroup diff	Z= 4.87 (P < 0.00	001)		6), f²= 49	.5%	0.01 0.1 1 10 Favours [experimental] Favours [control]
otal events eterogeneity: Tau ² = 0.0 est for overall effect: Z = est for suborouo differer	4; Chi [#] = 4; 3.22 (P = 0	.001)	23 (P =					Test for overall effect.	Z= 4.87 (P < 0.00	001)		6). (² = 49	5%	
eterogeneity: Tau ² = 0.0 ist for overall effect: Z = ist for suboroup differer	4; Chi ² = 4; 3.22 (P = 0 ices: Chi ² : Experim	0.001) = 0.13. d	23 (P = f = 1 (P = Contr	0.72). ol	I ^e = 0%	Odds Ratio	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect. Test for subarous diff B	Z = 4.87 (lerences: I Experime	P < 0.00 Chi ² = 1.	001) 98. df = 1 Control	(P = 0.1	(Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
derogeneity: Tau ^a = 0.0 st for overall effect Z = st for suboroup differer	4; Chi ² = 4; 3.22 (P = 0 ices: Chi ² : Experime Events	0.001) = 0.13. d	23 (P = f = 1 (P = Contr	0.72). ol	I ^e = 0%		avours (experimental) Favours (control)	Test for overall effect. Test for suboroup diff	Z = 4.87 (lerences: I Experime	P < 0.00 Chi ² = 1.	001) 98. df = 1 Control	(P = 0.1	(Favours [experimental] Favours [control]
terogeneity Tau ^s = 0.0 st for overall effect Z = st for suboroup differer udy or Subgroup .1 population-based e	4; Chi ² = 4; 3.22 (P = 0 ices: Chi ² : Experime Events	0.001) = 0.13. d	23 (P = f = 1 (P = Contr	0.72). ol	I ^e = 0%	Odds Ratio M.H. Random, 95% Cl 1.79 (1.03, 3.12)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect. Test for suboroup diff B <u>Study or Subprosp</u> 3.5.1 sCRC Oree(2003)	Z = 4.87 (erences: 1 Experime Events 427	P < 0.00 Chi ² = 1. ental <u>Total E</u> 569	001) 98. df = 1 Control Events T 237	(P = 0.1 otal We	ight M-H.	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55)	Favours [experimental] Favours [control] Odds Ratio
terogeneity: Tau ^s = 0.0 st for overall effect Z = st for suboroup differer 4.1 population-based e avatati(2014) nog(2005)	t, Chi ² = 4, 3.22 (P = 0 ces. Chi ² : Experime Events tudy(PB) 49 199	1.001) = 0.13. d ental <u>Total</u> 103 254	23 (P = f= 1 (P = Contr Events 36 89	0.72). ol <u>Total</u> 107 101	P=0% Weight 1 2.6% 2.0%	Odds Ratio M.H. Random, 95% CI 1.79 (1.03, 3.12) 0.49 (0.25, 0.96)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect. Test for subarouo diff B <u>Study or Subaroup</u> 3.5.1 sCRC Oneu(2003) Hong(2003)	Z = 4.87 (lerences: (Experimo Events 427 199	P < 0.00 Chi ² = 1.1 ental <u>Total E</u> 569 254	001) 98. df = 1 Control Events T 237 89	(P = 0.1 otal We 327 4 101 2	(<u>ight M-H.</u> 5% 9%	0dds Ratio Random, 95% CI 1.14 [0.84, 1.55] 0.49 [0.25, 0.96]	Favours [experimental] Favours [control] Odds Ratio
terogeneithy Tau ² = 0.0 st for overall effect Z = st for suboroup differer in the suboroup of suboroup int population-based et vatalic(2014) ng(2005) g(2008)	t, Chi ² = 4; 3.22 (P = 0 ces: Chi ² : Experime Events tudy(PB) 49 199 93	1.001) = 0.13. d ental <u>Total</u> 103 254 104	23 (P = f= 1 (P = Contr Events 36 89 164	0.72). ol <u>Total</u> 107 101 205	P=0% Weight 1 2.6% 2.0% 1.8%	Odds Ratio M.H. Random, 95% CI 1.79 (1:03, 312) 0.49 (0.25, 0.96) 2.11 (1:04, 4.31)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect. Test for subaroup diff B <u>Stady or Subaroup</u> 3.5.1 sCRC Oneu(2003) Hong(2005) Huang(2006)	Z = 4.87 (lerences: l Experime Events 427 199 705	P < 0.00 Chi ² = 1.1 <u>Total E</u> 569 254 831	001) 98. df = 1 Control Events T 237 89 853 1	(P = 0.1 otal We 327 4 101 2 052 4	(1011 M-H. 5% 9% 7%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67)	Favours [experimental] Favours [control] Odds Ratio
terogeneity, Tau ⁺ = 0.0 st for overall effect Z = st for suboroup differen i.t population-based + vvatat(2014) mp(2005) (g(2008) mp(2001)	4, Chi ² = 4, 3.22 (P = 0 ices: Chi ² : Experime Events itudy(PB) 49 199 93 120	ental Total 103 254 104 156	23 (P = f= 1 (P = Contr Events 36 89 164 107	0.72). ol <u>Total</u> 107 101 205 152	P=0% Weight 1 2.6% 2.0% 1.8% 3.0%	Odds Ratio M.H. Random, 55% CI 1.79 (1.03, 3.12) 0.49 (0.25, 0.96) 2.11 (1.04, 4.31) 1.40 (0.84, 2.33)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect. Test for suboroup off B <u>Stuck or Suboroup</u> 3.5.1 sCRC Gewc/000) Horg(2006) Hang(2006) Kanaan(2010)	Z = 4.87 (lerences: I Experime Events 427 199 705 56	P < 0.00 Chi ² = 1.1 Chi ² = 1.1 <u>Total 1</u> 569 254 831 75	001) 98. df = 1 Control Events T 237 89 853 1 69	(P = 0.1 otal We 327 4 101 2 052 4 93 2	(ight M-H. 5% 9% 7% 8%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06)	Favours [experimental] Favours [control] Odds Ratio
terogeneity: Tau ² = 0.0 st for overall effect Z = st for subaroux differer	4, Chi ² = 4, 3.22 (P = 0 ices: Chi ² : Experime Events itudy(PB) 49 199 93 120 205	ental Total 103 254 104 156 315	23 (P = f= 1 (P = <u>Events</u> 36 89 164 107 172	0.72). ol <u>Total</u> 107 101 205 152 245	P=0% Weight 1 2.6% 2.0% 1.8% 3.0% 4.7%	Odds Ratio M.H. Random, 95% CI 1.79 (1.03, 3.12) 0.49 (0.25, 0.96) 2.11 (1.04, 4.31) 1.40 (0.84, 2.33) 0.79 (0.55, 1.13)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subarous diff B 3.5.1 st CRL Onew(2002) Hong(2008) Hang(2008) Hang(2008) Levels(2003)	Z = 4.87 (lerences: I Experime Events 427 199 705 56 110	P < 0.00 Chi ² = 1.1 chi ² = 1.1 <u>Total I</u> 569 254 831 75 161	001) 98. df = 1 Control Events T 237 89 853 1 69 129	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3	(ight M-H, 5% 9% 7% 8% 9%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.33 (0.51, 2.06) 1.40 (0.91, 2.16)	Favours [experimental] Favours [control] Odds Ratio
terogeneity: Tau ² = 0.0 st for overall effect Z = st for subaroup differer st or <u>Subaroup</u> .1 population-based (vatal(2014) .9(2008) .9(2008) Marchand(2003)	4, Chi ² = 4, 3.22 (P = 0 ices. Chi ² Experime Events tudy(PB) 49 199 93 120 205 395	ental 103 254 104 156 315 504	23 (P = f= 1 (P = <u>Events</u> 36 89 164 107 172 460	0.72). ol <u>Total</u> 107 101 205 152 245 624	P=0% Weight 1 2.6% 2.0% 3.0% 4.7% 6.1%	Odds Ratio M.H. Random, 95% CI 1.79 (1.03, 3.12) 0.49 (0.25, 0.96) 2.11 (10.4, 4.31) 1.40 (0.84, 2.33) 0.79 (0.55, 1.13) 1.29 (0.98, 1.70)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for suboroup off B <u>Study or Suboroup</u> 3.5.1 sCRC Greu(2003) Hang(2005) Hang(2005) Hang(2005) Lang(2110) Leve(2003) Lau(2013)	Z = 4.87 (erences: 1 Experime Events 427 199 705 56 110 104	P < 0.00 Chi ² = 1.1 Chi ² = 1.1 Chi ² = 1.1 S69 254 831 75 161 125	001) 98. df = 1 Control Events T 237 89 853 1 69 129 80	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3 118 3	(ight M.H. 5% 9% 7% 8% 9% 2%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06) 1.36 (1.26, 1.26) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32)	Favours [experimental] Favours [control] Odds Ratio
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letogeneity Tau ⁴ = 0.0 1 for overall effect Z = 1 for suborous differen- 1 population-based et valati(2014) np(2005) (2008) np(2001) user(ang(2000) Marchand(2003) (2010)	4, Chi ² = 4, 3.22 (P = 0 ices. Chi ² Experime Events tudy(PB) 49 199 93 120 205 395	ental Total 103 254 104 156 315 504 373	23 (P = f= 1 (P = <u>Events</u> 36 89 164 107 172 460 678	0.72). ol <u>Total</u> 107 101 205 152 245 624 838	P=0% Weight 1 2.6% 2.0% 3.0% 4.7% 6.1%	Odds Ratio II.H. Random, 95% CI 1, 79 (1 03, 3 12) 0.49 (0 25, 0.89 1, 11 (1 04, 4 31) 1.40 (0.84, 2 33) 0.79 (0.55, 1 13) 1.29 (0.80, 1.70) 1.10 (0.80, 1.51) 1.52 (0.83, 2.51)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for suboroup off B <u>Study or Suboroup</u> 3.5.1 sCRC Greu(2003) Hang(2005) Hang(2005) Hang(2005) Lang(2110) Leve(2003) Lau(2013)	Z = 4.87 (erences: 1 Experime Events 427 199 705 56 110 104	P < 0.00 Chi ² = 1.1 Chi ² =	001) 98. df = 1 Control Events T 237 89 853 1 69 129 80 67	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3 118 3 101 3	(ight M.H. 5% 9% 7% 8% 9% 2% 1%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06) 1.36 (1.26, 1.26) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32)	Favours [experimental] Favours [control] Odds Ratio
letogeneity Tauf= 0.0 1 for overall effect Z = 1 for suboroup -1 population-based + vataliz2014) ng(2005) ng(2001) ng(2001) ng(2001) mer(2008) Marchand(2003) (2010) ter(2002) test-Hensch(2006)	t, Chi ² = 4, 3.22 (P = 0 ces: Chi ² : tudy(PB) 49 199 93 120 205 395 307 75 249 244	ental Total 103 254 104 156 315 504 373 100 334 300	23 (P = f=1 (P = Contr Events 36 89 164 107 172 460 678 678 678 111 962	0.72). ol <u>Total</u> 107 101 205 152 245 624 838 101 171 1169	P=0% Weight 1 2.6% 2.0% 4.7% 6.1% 5.4% 2.3% 4.2% 5.2%	Odds Ratio II.H. Random (5% CT 1.79 (1 02, 3 12) 0.49 (0.25, 0.68) 2.11 (1 04, 4 31) 1.40 (0.24, 2 13) 1.40 (0.24, 2 13) 1.29 (0.56, 1.70) 1.10 (0.80, 1.51) 1.59 (1 06, 2.38) 0.59 (1 06, 1.30)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for suboroup diff B Study or Suboroup 3.5.1 sCRC Crew(2003) Hang(2006) Kanaan(2010) Levis(2003) Levis(2003) Levis(2013) MeX/ay(2000) Subtratic (SS-CD) Total events Heterogenetit Tau*=0.0	Z = 4.87 (lerences: (Experime Events 427 199 705 56 110 104 75 1676 06; Chi# = 1	P < 0.00 Chi ² = 1.1 ental <u>Total 1</u> 569 254 831 75 161 125 100 2115	001) 98. df = 1 Control Events 1 237 89 853 1 69 129 80 67 2 1524	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3 118 3 101 3 005 25	(1991 M-H. 5% 9% 9% 9% 2% 1% 1%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32) 1.52 (0.83, 2.81)	Favours [experimental] Favours [control] Odds Ratio
lerogeneity: Tau ² = 0.0 it for overall effect Z = it for subbroup subbro	t, Chi ² = 4, 3.22 (P = 0 tees: Chi ² : tudy(PB) 49 199 93 120 205 395 307 75 249 244 111	ental Total 103 254 104 156 315 504 373 300 334 300 130	23 (P = f= 1 (P = Contr Events 36 89 164 107 172 460 678 677 111 962 119	0.72). 107 101 205 152 245 624 838 101 171 1169 160	P=0% Weight 1 26% 20% 18% 3.0% 4.7% 5.4% 2.3% 4.2% 5.2% 2.3%	Odds Ratio II JA Ranform, 55% C1 1.79 (1 00, 3.12) 0.49 (0.25, 0.88) 2.11 (1 0.4, 43) 1.40 (0.84, 233) 0.79 (0.55, 1.13) 1.40 (0.84, 233) 0.79 (0.55, 1.13) 1.10 (0.80, 1.51) 1.50 (1.06, 2.38) 0.40 (0.64, 1.33) 0.40 (0.64, 1.33)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subarous diff B 3.5.1 stCRC Onev(2003) Hong(2006) Hang(2006) Hang(2006) Lave(2003) Lave(Z = 4.87 (lerences: (Experime Events 427 199 705 56 110 104 75 1676 06; Chi# = 1	P < 0.00 Chi ² = 1.1 ental <u>Total 1</u> 569 254 831 75 161 125 100 2115	001) 98. df = 1 Control Events 1 237 89 853 1 69 129 80 67 2 1524	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3 118 3 101 3 005 25	(1991 M-H. 5% 9% 9% 9% 2% 1% 1%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32) 1.52 (0.83, 2.81)	Favours [experimental] Favours [control] Odds Ratio
lerogeneith; Tauf= 0.0 st for overall effect Z = st for suboroup different . t population based + vatati(2014) ng(2005) ng(2006) harchang(2001) Marchang(2003) ng(2008) harchang(2003) ng(2008) harchang(2003) netr(2002) meer(2013) netr(2013)	t, Chi ² = 4, 3.22 (P = 0 toes: Chi ² : tudy(PB) 49 199 93 120 205 395 307 75 249 244 111 485	001) = 0.13. d = 0.1	23 (P = f= 1 (P = Contr Events 36 89 164 107 172 460 678 677 111 962 119 962	0.72). tol Total 107 101 205 624 838 101 171 1169 160 1237	P=0% Weight 1 2.6% 2.0% 1.8% 3.0% 4.7% 5.4% 2.3% 4.2% 5.2% 6.8%	Odds Ratio II.H. Random 55% CT 1.79 (1 02, 31 2) 0.45 (0.25, 0.96) 2.11 (1 04, 4 31) 1.40 (0.84, 2 33) 0.79 (0.55, 1.13) 1.29 (0.86, 1.70) 1.10 (0.80, 1.51) 1.52 (0.83, 2.81) 1.55 (1 06, 1.30) 2.04 (1 06, 1.30) 2.04 (1 06, 3.30)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for suboroup diff B Study or Suboroup 3.5.1 sCRC Grew(2003) Hang(2006) Hang(2006) Hang(2010) Levis(2003) Levis(2003) Levis(2003) Mick/ay(2000) Subtratic (5%-CI) Total events Heterogenetic Turk= 01 Test for overall effect Z =	Z = 4.87 (lerences: (Experime Events 427 199 705 56 110 104 75 1676 06; Chi# = 1	P < 0.00 Chi ² = 1.1 ental <u>Total 1</u> 569 254 831 75 161 125 100 2115	001) 98. df = 1 Control Events 1 237 89 853 1 69 129 80 67 2 1524	(P = 0.1 otal We 327 4 101 2 052 4 93 2 213 3 118 3 101 3 005 25	(1991 M-H. 5% 9% 9% 9% 2% 1% 1%	0dds Ratio Random, 95% CI 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.03 (0.51, 2.06) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32) 1.52 (0.83, 2.81)	Favours [experimental] Favours [control] Odds Ratio
Interpreter TauF= 0.0 Interpreter TauF= 0.1 Interpreter Tau Interpreter	t, Chi ² = 4, 3.22 (P = 0 toes. Chi ² : tudy(PB) 49 199 93 120 205 395 307 75 249 244 111 485 378	001) ental Total 103 254 104 315 504 373 100 334 300 130 610 498	23 (P = f=1 (P = Contr Events 36 89 164 107 172 2460 678 677 111 962 119 973 453	0.72). ol <u>Total</u> 107 101 205 152 245 624 838 101 171 1169 160 1237 600	P=0% 2.6% 2.0% 1.8% 3.0% 4.7% 6.1% 5.4% 5.2% 2.3% 6.2% 5.2% 5.2% 6.8% 6.1%	Odds Ratio 1.79 (1 00, 3.12) 0.48 (2 0, 0.12) 0.49 (2 0, 0.12) 0.49 (2 0, 0.12) 1.79 (2 0, 0.23) 1.99 (0, 0.12) 1.99 (0, 0.12)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subaroup diff B <u>Start or Subaroup</u> 3.5.1 sCRC 0ew/2003) Horg(2005) Hung(2005) Law(Z = 4.87 (lerences: i Experime Events 427 199 705 56 110 104 75 1676 06; Chi ² = 1 1.65 (P = 1	P < 0.00 Chi ² = 1: <u>Total E</u> 569 254 831 161 125 100 2115 312, df= 0.10)	001) 98. df = 1 Control Events 1 237 89 853 1 69 129 80 67 2 1524 6 (P = 0.0	(P = 0.1 otal Wee 327 4 101 2 213 3 101 3 101 3 105 25 04); P = 5	ight M-H. 5% 5% 9% 7% 8% 9% 2% 1% 1% 1%	0dds Ratio Random, 25% Cl 1.14 (0.84, 1.55) 0.49 (0.25, 0.96) 1.31 (1.02, 1.67) 1.33 (0.57, 2.06) 1.40 (0.91, 2.16) 2.35 (1.26, 4.32) 1.52 (0.83, 2.81) 1.52 (0.85, 1.60)	Favours [experimental] Favours [control] Odds Ratio
strogenet), Tau#= 0.0 (for overall effect Z = (for subarue different strong Subarue different strong Subarue different stratigization (group)	t, Chi ² = 4, 3.22 (P = 0 toes: Chi ² : tudy(PB) 49 199 93 120 205 395 307 75 249 244 111 485	001) = 0.13 d ental Total 103 254 104 156 315 504 315 504 333 100 334 300 610 498 345	23 (P = f= 1 (P = Contr Events 36 89 164 107 172 460 678 677 111 962 119 962	0.72). 107 101 205 152 245 624 838 101 171 1169 160 1237 600 670	P=0% Weight 1 2.6% 2.0% 3.0% 4.7% 6.1% 5.4% 2.3% 4.2% 2.3% 6.8% 6.1% 5.0%	Odds Ratio II.H. Random 95% CT 1.79 (1 00, 3 1 2) 0.45 (0.25, 0.96) 2.11 (1 04, 4 3) 1.40 (0.24, 2 3) 0.79 (0.25, 1.13) 1.10 (0.05, 1.13) 1.50 (0.05, 1.13) 1.50 (0.05, 1.21) 1.50 (0.05, 1.21) 0.94 (0.06, 1.30) 2.01 (1.0, 3.04) 1.05 (0.03, 1.34) 1.05 (0.07, 1.47)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subarous diff B Study or Subarous 3.5.1 sCRC Oneu(2003) Hang(2006) Hang(2006) Hang(2006) Hang(2010) Levis(2003) Levis(2003) Levis(2003) Levis(2003) Mel/ay(2006) Substate(55+CQ) Total events Heterogenet/Tau*=01 Test for overall effect 2= 3.5.2 HIPCC Baa(2001)	Z = 4.87 (lerences: 1 Experime Events 427 199 705 566 110 104 75 1676 06; ChiP = 1 = 1.65 (P = 1	P < 0.00 Chi ² = 1. <u>Total I</u> 569 254 831 75 161 125 100 2115 3.12, df = (3.12, df = (3.12, df = (3.12, df =))	001) 98. df = 1 Control Events T 237 89 653 1 69 67 2 1524 6 (P = 0) 139	(P = 0.1 otal We 327 4 93 2 213 3 101 3 101 3 101 3 105 25 04), P = 5 186 3	ight M.H. 5% 9% 7% 8% 9% 2% 1% 1% 1% 1%	065 Ratio Random, 95% CI 114 (0 84, 155) 064 (0 24, 0 84) 131 (1 02, 167) 131 (1 02, 167) 132 (5 2, 266) 134 (1 02, 126) 131 (2 0, 167) 132 (5 2, 0 82, 21) 132 (1 0, 167) 132 (1 0, 167)	Favours [experimental] Favours [control] Odds Ratio
erogeneity Tau# = 0.0 for overall effect 2 = for subscrup dv or Subscrup d	4, Chi ² = 4, 3.22 (P = 0 ces: Chi ² = <u>Experime</u> <u>Expertime</u> 49 93 120 205 395 249 244 111 485 378 224	001) ental Total 103 254 104 315 504 373 100 334 300 130 610 498	23 (P = f=1 (P = Contri Events) 36 89 164 89 107 172 460 678 677 111 962 119 973 547	0.72). ol <u>Total</u> 107 101 205 152 245 624 838 101 171 1169 160 1237 600	P=0% 2.6% 2.0% 1.8% 3.0% 4.7% 6.1% 5.4% 5.2% 2.3% 6.2% 5.2% 5.2% 6.8% 6.1%	Odds Ratio 1.79 (1 00, 3.12) 0.48 (2 0, 0.12) 0.49 (2 0, 0.12) 0.49 (2 0, 0.12) 1.79 (2 0, 0.23) 1.99 (0, 0.12) 1.99 (0, 0.12)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subarous diff B <u>Start or Subarous</u> 3.5.1 sCRC Onev(2003) Hexp(2005) Hexp(2005) Hexp(2005) Hexp(2005) MeXap2(200) Subaroat (BSA CI) Total events Heterogenetity Tau*a DI Test or overall effect Z = 3.5.2 HIPCC Basis(2001) Kong(2000)	Z = 4.87 (lerences: i Experime Events 427 199 705 56 110 104 765 1676 1676 1676 1676 1676 1676 1676	P < 0.00 Chi ² = 1. <u>Total I</u> 569 254 831 75 105 2145 1312, df = 1312, df = 1312, df = 146 49	001) 98. df = 1 237 89 853 1 69 80 67 2 1524 6 (P = 0.) 139 27	(P = 0.1 otal We 327 4 101 2 213 3 110 3 101 3 101 3 105 25 104), P = 5 186 3 37 1	(10.11 M-H. 5% 9% 9% 9% 2% 1% 1% 4% 7% 8%	bdds Ratio Rattion, 85% CT 114 (0.84, 155) 0.49 (0.22, 0.86) 1.31 (0.02, 167) 1.83 (0.52, 2.06) 1.83 (0.52, 2.06) 1.83 (0.52, 2.06) 1.83 (0.52, 2.06) 1.83 (0.52, 2.06) 1.52 (0.82, 2.81) 1.52 (0.82, 2.81) 1.52 (0.82, 2.81) 1.52 (0.85, 1.66) 0.65 (0.40, 1.04) 1.65 (0.95, 4.58)	Favours [experimental] Favours [control] Odds Ratio
engeneity Tau# = 0.0 for overall effect 2 = for suboroup different population based et aux(2014) (2006) (2008) (2000)	4, Chi ² = 4, 3.22 (P = 0 cres: Chi ² = <u>Experimu</u> <u>Events</u> 49 93 120 205 93 120 205 307 75 5 307 249 244 111 14 8378 249 244 319	001) = 0.13 d = 0.13	23 (P = 23 (P = f=1 (P = Contr Events 36 89 164 107 172 460 87 107 111 962 973 453 547 4938	0 72). ol Total 107 101 205 152 245 624 838 101 171 1169 160 1237 600 670 6380	Weight 1 2.6% 2.0% 1.8% 3.0% 4.7% 6.1% 5.4% 2.3% 6.8% 6.1% 5.0% 5.0% 5.7.5%	Odds Ratio II.H. Random 95% CT 1.79 (1 00, 3 1 2) 0.45 (0.25, 0.96) 2.11 (1 04, 4 3) 1.40 (0.24, 2 3) 0.79 (0.25, 1.13) 1.10 (0.05, 1.13) 1.50 (0.05, 1.13) 1.50 (0.05, 1.21) 1.50 (0.05, 1.21) 0.94 (0.06, 1.30) 2.01 (1.0, 3.04) 1.05 (0.03, 1.34) 1.05 (0.07, 1.47)	avours (experimental) Favours (control) Oddis Ratio	Test for overall effect Test for subarous diff B Study or Subarous 3.5.1 sCRC Oneu(2003) Hang(2006) Kanano(2010) Levis(2003) Levis(2003) Levis(2003) Levis(2003) Levis(2003) Substatic Ture = 0 Test for overall effect _z = 3.5.2 HIPCC Baa(2001) Kong(2000) Kouge(2006)	Z = 4.87 (lerences: 1 Experime revents 427 199 705 56 110 104 75 1676 1676 1676 96 40 205	P < 0.00 Chi ² = 1. <u>Total E</u> 569 254 831 75 161 125 100 2115 312, df= 0.10) 146 49 315	001) 98. df = 1 2017 2017 89 853 1 69 129 80 67 2 1524 6 (P = 0) 139 27 172	(P = 0.1 otal Wee 327 4 101 2 052 4 93 2 213 3 101 3 101 3 105 25 106 3 37 1 245 4	(0) (0)H M-H. 5% 9% 7% 8% 9% 9% 7% 4% 7% 8% 2%	065 Ratio Random, 95% CI 114 (D 84, 155) 048 (D 25, 048) 131 (D 02, 167) 133 (D 57, 206) 144 (D 98, 21, 68) 131 (D 02, 167) 132 (D 57, 206) 144 (D 98, 21, 68) 132 (D 28, 28) 132 (D 28, 2	Favours [experimental] Favours [control] Odds Ratio
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Figure 3. A, Meta-analysis of the association between CCND1 G870A polymorphism and CRC in Ethnicity. B, Meta-analysis of the association between CCND1 G870A polymorphism and CRC in location. C, Meta-analysis of the association between CCND1 G870A polymorphism and CRC in study design. D, Meta-analysis of the association between CCND1 G870A polymorphism and CRC in study design. D, Meta-analysis of the association between CCND1 G870A polymorphism and CRC in cancer type. CCND1 = cyclinD1, CRC = colorectal cancer.

D

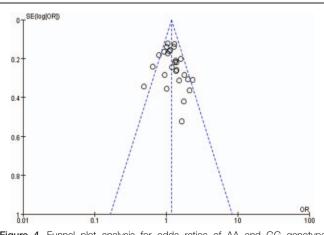


Figure 4. Funnel plot analysis for odds ratios of AA and GG genotype compared with GG genotype in overall studies.

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