RESEARCH COMMUNICATION

The Cyclin D1 G870A Polymorphism and Colorectal Cancer Susceptibility: A Meta-analysis of 20 Populations

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Abstract

Purpose: Studies of the association between the cyclin D1 (CCND1) G870A genetic polymorphism and risk of colorectal cancer (CRC) have generated conflicting results. In order to derive a more precise estimation, a meta-analysis was here performed. Materials and methods: An extensive search of relevant studies was carried out as a meta-analysis of twenty studies with 5,975 cases and 8,333 controls. Results: Overall, a significantly elevated colorectal cancer risk was associated with variant allele 870A when all studies were pooled (AA vs. GG: OR = 1.23, 95%CI = 1.04-1.44; GA vs. GG: OR = 1.13, 95%CI = 1.01-1.26; dominant model: OR = 1.16, 95%CI = 1.03-1.31). In the subgroup analysis by ethnicity, significantly increased risks were detected among Caucasians (AA vs. GG: OR = 1.27, 95%CI = 1.04-1.44; and dominant model: OR = 1.17, 95%CI = 1.02-1.34). With stratification into sporadic CRC and hereditary nonpolyposis colorectal cancer (HNPCC), the former demonstrated increased cancer susceptibility (AA vs. GG: OR = 1.24, 95%CI = 1.04-1.48; dominant model: OR = 1.17, 95%CI = 1.04-1.33). However, no significant associations were found in either Asians or HNPCC patients for any genetic model. Conclusion: The results suggest that the cyclin D1 870A allele is a low-penetrant risk factor for development of sporadic colorectal cancer, especially among Caucasians.

Keywords: CyclinD1 - polymorphism - colorectal cancer - meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cause of cancer-related mortality in the Western world, and in the United States, it represents the second most common cause of cancer death (Jemal et al., 2010). A recent study indicates that about 35 percent of all colorectal cancer can be ascribed to inherited genetic susceptibility (Lichtenstein et al., 2000), but exact mechanisms are not fully understood.

It has been suggested that low penetrance susceptibility genes combining with environmental factors may be important in the development of cancer (Lichtenstein et al., 2000). In recent years, the common functional polymorphism, G870A, in the gene encoding a key cell cycle regulatory protein, cyclinD1 (CCND1), has been widely studied as a possible low-penetrant susceptibility allele for a variety of cancers, and in particular, colorectal cancer. CyclinD1 regulates transition from G1 to the S phase during cell division. High activity of cyclinD1 leads to premature cell passage through the G1-S transition, resulting in propagation of minute damaged DNA and accumulation of genetic errors, therefore leading to selective advantage for abnormal cell proliferation (Hall and Peters, 1996). CyclinD1 G870A, which corresponds to codon 241 (Pro241-Pro), is a silent variant and does not result in an amino acid alteration within the protein sequence. However, CCND1 870A allele results in an alternatively spliced transcript of CCND1, called transcript b, which lacks PEST motif containing exon 5. PEST motif is critical for the degradation of cyclinD1; thus, transcript b (870A allele) has shown to have a longer half-life than the transcript a (G allele, the wild type gene.) encoded protein. This highly suggests that individuals with CCND1 870A are more likely to bypass the G1-S cell cycle checkpoint, thus contributing to cancer development (Solomon et al., 2003).

A number of studies have reported on roles of the CCND1 G870A polymorphism in colorectal cancer (Kong et al., 2000; McKay et al., 2000; Bala and Peltomaki, 2001; Kong et al., 2001; Porter et al., 2002; Grieu et al., 2003; Le Marchand et al., 2003; Hong et al., 2005; Huang et al., 2006; Jiang et al., 2006; Kruger et al., 2006; Probst-Hensch et al., 2006; Schernhammer et al., 2006; Forones et al., 2008; Grunhage et al., 2008; Jing et al., 2008; Talseth et al., 2008; Tan et al., 2008; Liu et al., 2010; Yaylim-Eraltan et al., 2010), but the results are conflicting rather than conclusive. Therefore, a meta-analysis was performed

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from all eligible studies to evaluate the association between CCND1 G870A polymorphism and colorectal cancer risk in this study.

Materials and Methods

Publication search

Medline database, EMBASE, Web of Science, and Chinese Biomedicine Database were searched comprehensively (last search was updated on Sep 10, 2010, using the search terms: "polymorphism", "cyclinD1", "CCND1," and "colorectal cancer".). And to minimize potential publication bias, there were no language and other restrictions. All searched studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. All retrieved articles were examined by reading the titles and abstracts, and the full texts of the potentially relevant publications were further checked for their suitability for this meta-analysis. When more than one of the same patient population was included in several publications, only the most recent or complete study was used.

Inclusion criteria

The inclusion criteria were: (a) evaluation of the CyclinD1 G870A polymorphism and Colorectal Cancer Risk, (b) case–control or nested case-control studies, and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence intervals (CIs). Accordingly, papers that could not offer the source of cases and controls or other essential information were excluded; reviews and repeated literatures were also excluded.

Data extraction

Information was carefully extracted from all eligible publications independently by two of the investigators according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author's surname, year of publication, ethnicity, cancer type, source of control, numbers of cases and controls with the AA, GA, and GG genotypes, respectively. Different ethnicity descents were categorized as Caucasian, Asian, and African. We did not define any minimum number of patients to include a study in our meta-analysis. Characteristics of individual studies were summarized in Table 1.

Statistical methods

To test for control population selective bias, the distribution of genotypes in control subjects of each individual population was tested for departure from Hardy-Weinberg equilibrium by means of the chi-square test (Guo and Thompson, 1992). Crude ORs with 95% CIs were used to assess the strength of association between the CyclinD1 G870A polymorphism and colorectal cancer risk. The pooled ORs were performed for codominant model (GA vs. GG; AA vs. GG), dominant model (GA/AA vs. GG), and recessive model (AA vs. GA/GG), respectively. Heterogeneity assumption was checked by the chi-square based Q-test (Cochran, 1954). A P value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel–Haenszel method) (Mantel and Haenszel, 1959). Otherwise, the random-effects model (the DerSimoian and Laird method) was used (DerSimonian and Laird, 1986). In order to evaluate the ethnicity and cancer type effects, subgroup analyses were performed by ethnicity group, HNPCC and sporadic CRC, respectively. Moreover, sensitivity analysis was performed excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy–Weinberg Equilibrium (HWE), given that the deviation may denote bias. For the assessment of the deviation from HWE, the appropriate Goodness-of-fit chi-square test was performed. The presence of publication bias was examined by visual inspection of funnel plots, and formally evaluated with Begg's adjusted rank correlation test and Egger's regression asymmetry test (Egger et al., 1997). Begg's test examines the correlation between the effect estimates and their variances. Egger's test is based on inverse-variance weighted regression of the effect sizes on their precision (the inverse of standard error) to test whether the intercept deviates significantly from zero. All the statistical tests were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA) and Review Manage (V5.0). All the P values were two-sided and $P < 0.05$ was considered representative of statistically significant.

Results

Study characteristics: A total of 20 publications met the inclusion criteria, and 5,975 cases and 8,333 controls were extracted to establish a database of the meta-analyses. Table 1 listed the studies identified and their main characteristics. Of the 20 studies, there were seventeen studies of Caucasians, seven studies of Asians and no study of Africans. All of the cases were histologically confirmed. Controls were mainly healthy populations and matched for age and/or sex. Genotypes distributions in the controls of all studies were tested. All studies indicated that the distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium except for one Asian study (Huang et al., 2006, p=0.004).

Main results: Table 2 shows the main results of this meta-analysis. Overall, significantly elevated colorectal cancer risk was associated with CyclinD1 870A allele when all studies were pooled into the meta-analysis (AA vs. GG: OR = 1.23, 95%CI = 1.04-1.44; GA vs. GG: OR = 1.13, 95%CI = 1.01-1.26; dominant model: OR = 1.16, 95%CI = 1.03-1.31). The forest plot of dominant model, namely, (GA/AA vs. GG), were showed in Figure 1a, Figure 1b and Table 2. In the subgroup analysis by ethnicity, significant increased risks were found for A allele carriers among Caucasians (AA vs. GG: OR = 1.27,

Table 1. Characteristics of Studies Included in this Meta-analysis

Author and year	First author's Country	Ethnicity	No. Cases	No. Controls	Type of Cancer	Source of Controls	HWE of Controls	MAF of Controls (%)
Yu 2003	China	Asian	321	345	EC	Healthy persons	0.35	42.5
Zhang 2003A	China	Asian	120	183	EC	Healthy persons	0.12	48.6
Liu 2010	American	Caucasian	312	454	EC	Healthy persons	0.37	40.9
Jain 2007	India	Caucasian	151	201	EC	-	0.11	46.0
Geddert 2005A	Germany	Caucasian	56	253	EC	Healthy persons	0.22	48.2
Casson 2005	Canada	Caucasian	56	95	EC	-	0.06	35.8
Zhang 2003B	China	Asian	120	183	GC	Healthy persons	0.12	48.6
Song 2007	Korea	Asian	253	442	GC	Healthy persons	0.62	48.6
Jia 2008	China	Asian	159	162	GC	Hospital patients	0.08	36.1
Tahara 2009	Japan	Asian	392	359	GC	Hospital patients	0.92	47.6
Geddert 2005B	Germany	Caucasian	286	253	GC	Healthy persons	0.22	48.2
Bala 2001	American	Caucasian	146	186	HNPCC	--	0.66	48.7
Grunhage 2007a	Germany	Caucasian	98	220	HNPCC	Hospital patients	0.96	47.1
Kong 2000	American	Caucasian	49	37	HNPCC	Healthy persons	0.51	44.6
Kruger 2006	Germany	Caucasian	315	245	HNPCC	Healthy persons	0.95	45.5
Porter 2002a	UK	Caucasian	206	171	HNPCC	Hospital patients	0.75	41.2
Talseth 2008	Australia	Caucasian	157	153	HNPCC	Healthy persons	0.63	46.4
Hong 2005	Singapore	Asian	254	101	Sporadic CRC	Healthy persons	0.67	36.7
Huang 2006	Taiwan	Asian	831	1,052	Sporadic CRC	Hospital patients	0.004	41.9
jing 2008	China	Asian	104	205	Sporadic CRC	Hospital patients	0.16	47.5
Le Marchand 2003a	American	Asian	296	380	Sporadic CRC	Healthy persons	0.68	49.1
Le Marchand 2003b	American	Asian	138	161	Sporadic CRC	Healthy persons	0.26	42.8
Liu 2010	China	Asian	373	838	Sporadic CRC	Healthy persons	0.33	44.7
Probst-Hensch 2005	Switzerland	Asian	300	1169	Sporadic CRC	Healthy persons	0.28	41.1
Forones 2008	Brazil	Caucasian	123	120	Sporadic CRC	Healthy persons	0.19	43.8
Grunhage2007b	Germany	Caucasian	96	220	Sporadic CRC	Hospital patients	0.96	47.0
Jiang 2006	Japan	Caucasian	301	291	Sporadic CRC	Hospital patients	0.91	44.1
Kong 2001	American	Caucasian	321	152	Sporadic CRC	Healthy persons	0.14	42.8
Le Marchand 2003c	American	Caucasian	70	83	Sporadic CRC	Healthy persons	0.34	42.5
McKay 2000	UK	Caucasian	100	101	Sporadic CRC	Healthy persons	0.85	41.6
Porter 2002b	UK	Caucasian	128	171	Sporadic CRC	Hospital patients	0.75	41.2
Schernhammer 2006	American	Caucasian	610	1,237	Sporadic CRC	Healthy persons	0.25	44.3
Tan 2008	Germany	Caucasian	498	600	Sporadic CRC	Healthy persons	0.46	49.7
Yaylim-Eraltan 2010	Turkey	Caucasian	57	117	Sporadic CRC	Hospital patients	0.85	49.6

GC, gastric cancer; EC, esophageal cancer; CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; MAF,minor allele frequency; HWE, Hardy–Weinberg equilibrium; a,b,c different populations in one study; d focused on sporadic CRC; A,B different cancer type in one study

Table 2. Main Results for Odds Ratios (ORs) and 95%Confidence Intervals (CIs) in the Meta-analysis

CCND1 G870A		AA vs. GG		GA vs. GG		Dominant model		Recessive model	
		OR 95% CI	I2	OR 95% CI	I2	OR 95% CI	I2	OR 95% CI	I2
Ethnicity	Asian	1.06 (0.83-1.34)	66.1	1.02 (0.83-1.26)	62.9	1.03 (0.84-1.27)	67.0	1.02 (0.91-1.14)	23.2
	Caucasian	1.29 (1.07-1.55)	53.8	1.13 (1.01-1.28)	23.0	1.18 (1.04-1.33)	35.3	1.18 (1.01-1.38)	58.9
Type of cancer	EC	1.50 (0.89-2.51)	55.1	1.13 (0.82-1.55)	63.5	1.22 (0.86-1.74)	62.9	1.29 (0.92-1.80)	53.5
	GC	0.86 (0.60-1.23)	53.2	0.93 (0.66-1.32)	40.8	0.92 (0.66-1.27)	48.2	0.91 (0.69-1.20)	45.1
	CRC	1.23 (1.04-1.44)	74.7	1.12 (0.99-1.27)	49.3	1.15 (1.02-1.31)	62.3	1.12 (1.00-1.25)	65.4
	Total	1.19 (1.03-1.37)	58.8	1.09 (0.98-1.22)	44.1	1.12 (1.01-1.25)	51.9	1.10 (1.00-1.22)	50.1
Subgroup analysis of CRC	HNPCC	1.17 (0.74-1.84)	61.2	1.09 (0.79-1.49)	47.1	1.13 (0.80-1.61)	60.7	1.11 (0.83-1.47)	36.1
	Sporadic	1.24 (1.04-1.48)	53.2	1.15 (1.02-1.29)	26.7	1.17 (1.04-1.33)	36.9	1.11 (0.98-1.27)	50.8
	Asian	1.15 (0.86-1.54)	61.8	1.13 (0.86-1.49)	62.5	1.13 (0.87-1.48)	64.2	1.04 (0.90-1.19)	24.6
	Caucasian	1.27 (1.04-1.56)	52.2	1.12 (1.00-1.26)	8.8	1.17 (1.02-1.34)	32.4	1.17 (0.99-1.38)	52.8

I-squared (%), the variation in OR attributable to heterogeneity; Random-effects model was used when I2 >50% for heterogeneity test; otherwise, fixed-model was used

95%CI = 1.04-1.44; dominant model: OR = 1.17, 95%CI = 1.02-1.34) No significant increased risk was found among Asians .When subgroup analysis stratified into HNPCC and sporadic CRC, an increased risk was seen in sporadic CRC with A allele carriers (AA vs. GG: OR = 1.24, 95%CI = 1.04-1.48; dominant model: OR = 1.17, 95%CI = 1.04-1.33). However, no significant association was observed in HNPCC cases. Examining genotype frequencies in controls, significant deviation from HWE was detected in one study, namely, the Asian part of the study by Huang et al. (Sensitivity analysis was performed, and after the exclusion of this study the results remained unchanged.

Publication bias: The shapes of the funnel plot did not reveal any evidence of obvious asymmetry. The funnel

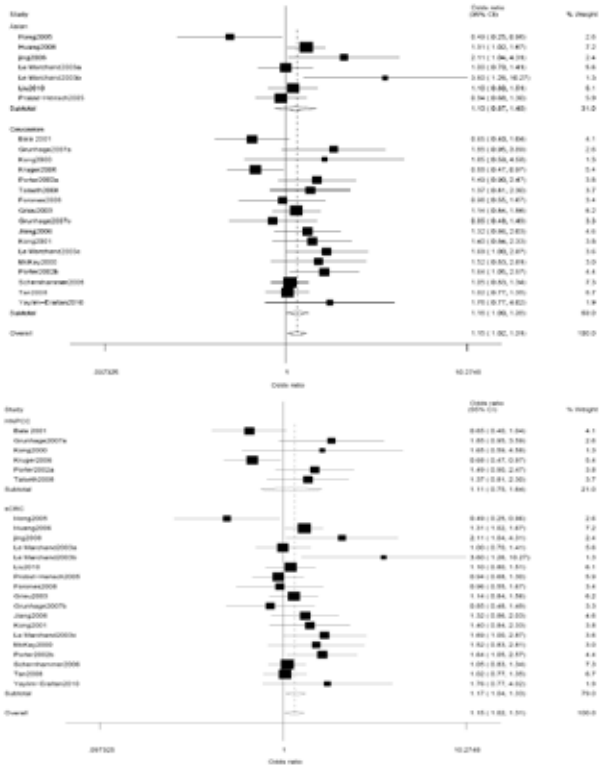

Figure 1. Forest Plots of Colorectal Cancer Risk Associated with the A Variant Genotype for Dominant Model (GA/AA vs. GG). a) Overall Studies and Stratified by Ethnics. b) HNPCC and Sporadic CRC Risk

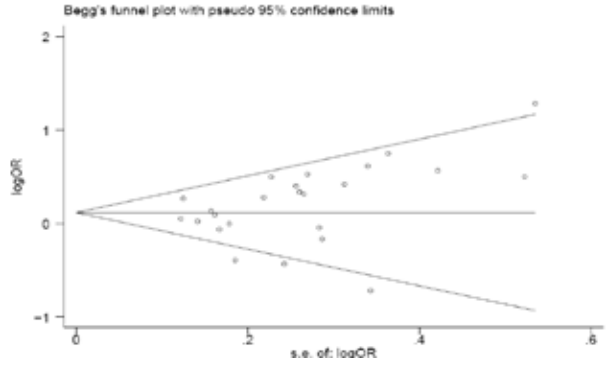

Figure 2. Funnel Plot Analysis for Odds Ratios of GA/AA Genotype Compared with GG Genotype in Overall Studies

plot of dominant model was given in Figure 2. Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias (P = 0.08 for AA vs. GG; P = 0.22 for GA vs. GG; P = 0.107 for dominant model, and P = 0.19 for recessive model, respectively).

Discussion

Colorectal cancer (CRC) is one of the most common causes for death from malignancies in Western societies. Both sporadic and hereditary CRC is caused by a set of molecular events (Tejpar and Van Cutsem, 2002). It has been reported that amplification of CCND1 and altered expression of the protein are associated with cell proliferation and poor prognosis in a variety of tumors, including head and neck, colon and rectum, breast, lung (Donnellan and Chetty, 1998; Palmqvist et al., 1998). But results of case-control studies about this genetic polymorphism were inconsistent. So a meta-analysis was performed to examine the association between CyclinD1 G870A Polymorphisms and colorectal cancer risk. We found A allele significantly elevated colorectal cancer risk in codominant and dominant models, which was in agreement with Tan et al., (2008). When stratified by ethnics, significant associations were found in Caucasians but not for Asians, suggesting a possible role of ethnic differences in genetic background and being modified by environmental facts (Donnellan and Chetty, 1998; Palmqvist et al., 1998). Environmental factors include age, gender, diet, smoking, alcohol consumption, ethnicity, NSAIDS use, BMI, and so on. It was inferred that there must be interaction between the environmental factors and CyclinD1 gene, which had been proved in many researches, including the studies listed in Table 1. Therefore, interaction is one of the factors of the meta-analyses. Because of lack detail data, we had to given up performing a meta-regression. In addition, the influence of the A allele might be masked by the presence of other as-yet unidentified causal genes involved in colorectal cancer development in Asians. Furthermore, it is also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate (Wacholder et al., 2004). Of note, in the subgroup study of HNPCC and sporadic CRC, no significant association was found in HNPCC patients when pooled. As we know autosomal dominantly inherited hereditary nonpolyposis colorectal cancer (HNPCC) is caused by germ line mutations in the DNA mismatch repair (MMR) genes, mainly MSH2 and MLH1 (Liu et al., 1996). Studies are needed to identify modifying factors of HNPCC phenotype, which may contribute to a more detailed risk assessment. Considering the limited studies and population numbers of HNPCC included in the meta-analysis, our results should be interpreted with caution. Heterogeneity is a potential problem when interpreting the results of all meta-analyses (Munafo and Flint, 2004). Significant between-study heterogeneity existed when all study pooled (Table 2). After subgroup analyses by ethnicity, the heterogeneity was effectively decreased for Caucasians. The reason might be that differences of genetic backgrounds and the environment existed among different ethnicities.

Some limitations of this meta-analysis should be acknowledged. First of all, the controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some studies enrolled inpatient with benign disease. Therefore, non-differential misclassification bias was possible because these studies may have included the control groups who have different risks of developing colorectal cancer. Second, our meta-analysis was based on unadjusted estimates, while a more precise analysis might be conducted if individual data were available, which could allow for an adjustment estimate by sex, age, and lifestyle such as smoking, alcohol drinking, body weight . In spite of these, our meta-analysis also

had some advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias was detected; indicating that the whole pooled result may be unbiased.

In summary, this meta-analysis found that cyclinD1 870A is a low-penetrant risk factor for developing colorectal cancer in Caucasians. Large studies with the pooling of individual data should be considered in future association studies to verify results from this meta-analysis and to further evaluate the effect of gene-gene and gene–environment interactions on the cyclinD1 G870A polymorphism-associated colorectal cancer risk.

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