Investigation of *cyclin D1* rs9344 G>A polymorphism in colorectal cancer: a meta-analysis involving 13,642 subjects

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**Abstract:** The relationship between *cyclin D1* (CCND1) rs9344 G>A polymorphism and colorectal cancer (CRC) risk is still ambiguous. To obtain a precise estimation of the relationship, we performed an extensive meta-analysis based on the eligible studies. Crude odds ratios with their 95% confidence intervals were harnessed to determine the strength of correlation between *CCND1* rs9344 G>A polymorphism and CRC risk under the allele, the homozygote, the dominant, and the recessive genetic models, respectively (28 studies with 5,784 CRC cases and 7,858 controls). Our results indicated evidence of the association between *CCND1* rs9344 G>A polymorphism and the increased risk of CRC in four genetic models: A vs G, AA vs GG, AA+GA vs GG, and AA vs GA+GG. In a stratified analysis by cancer type of CRC, there was an increased risk of sporadic CRC found in three genetic models: A vs G, AA vs GG, and AA+GA vs GG. In a stratified analysis by ethnicity, there was an increased CRC risk found among Asians in allele comparison genetic models, as well as Caucasians in two genetic models: AA+GA vs GG and A vs T. In summary, this meta-analysis demonstrates that *CCND1* rs9344 G>A polymorphism may be a risk factor for CRC.

**Keywords:** polymorphism, CCND1, colorectal cancer, susceptibility, meta-analysis

**Introduction**

In 2012, colorectal cancer (CRC) is the third and second most commonly diagnosed malignancy in males and females, respectively, worldwide, with an estimated 1,360,600 new CRC cases and 693,900 CRC-related mortality occurring annually.1 This type of malignancy involves a more frequent sporadic CRC (sCRC) and a less frequent hereditary form. The increasing CRC incidence and mortality rate have been attributed to an increasingly “Westernized lifestyle,” including a decreased consumption of dietary fiber, drinking, smoking, overweight, and being physically inactive.2 However, the etiology of CRC is very complicated. A number of altered environmental and genetic factors have been considered as risk factors for CRC.3,4 Recently, a previous study showed that ~35% of CRC patients could be attributed to certain inherited genetic risk factors.5 Identification of these important genetic risk factors correlated with CRC may enrich our view of this complex disease.

The *cyclin D1* (CCND1) gene located on chromosome 1q31-32. CCND1 is an important protein for the regulation of the G1–S phase transition of cell cycle. Overexpression or disordered regulation of the *CCND1* gene will break the balance of cell cycle and might lead to abnormalities and consequently result in cellular transformation and malignancy. Recent studies showed that *CCND1* was overexpressed in CRC,
which was correlated with a poor clinical outcome and some clinicopathological characteristics.6,7

The human CCND1 gene is very polymorphic (http://www.ncbi.nlm.nih.gov/SNP). The CCND1 rs9344, a G to A polymorphism at nucleotide 870 in exon 4, increases the frequency of alternate splicing. Results of prior studies showed that the A allele of CCND1 rs9344 G>A resulted in an increasing level of mRNA (transcript-b) encoding CCND1 protein with an altered C-terminal domain.8,9 Results of some epidemiologic studies demonstrated that CCND1 rs9344 G>A polymorphism might confer CRC risk.10–18 Several meta-analyses showed that CCND1 rs9344 G>A polymorphism might be a risk factor for CRC, especially in the subgroups of sCRC and Caucasians.19–21 However, in these studies, as only a few case–control studies performed on the Asian populations, the power of these pooled analyses might be limited. Recently, more epidemiologic studies focusing on the relationship between CCND1 rs9344 G>A polymorphism and CRC risk were conducted among Asians. Considering the vital role of CCND1 rs9344 G>A polymorphism for CRC risk, an updated meta-analysis was needed to obtain a more precise assessment.

Materials and methods

Search strategy
PubMed and EMBASE online databases (updated to February 11, 2016) were searched using the corresponding keywords related to CCND1 rs9344 G>A polymorphism and CRC: cyclin D1 or CCND1; and polymorphism, variant, or single-nucleotide polymorphism; colorectal, rectal, or colon; and cancer, carcinoma, tumor, malignancy, or neoplasm. No language restriction was applied. We also searched the bibliography of reviews, meta-analyses, and all eligible articles to retrieve the potential publications.

Inclusion and exclusion criteria
The included studies were selected according to the major criteria as follows: 1) case–control studies; 2) the association of CCND1 rs9344 G>A polymorphism with CRC risk; 3) CRC cases diagnosed by histopathology; and 4) genotype frequencies to determine the pooled odds ratios (ORs) with their 95% confidence intervals (95% CIs). Accordingly, publications with insufficient data, reviews and meta-analyses, and comments were excluded.

Data extraction
For each included study, two authors (HQ and CC) extracted the data independently as follows: the first author’s surname; year of publication; country where the study was carried out; race (included Asians, Caucasians, and Mixed); the type of CRC (included hereditary non-polyposis colorectal cancer [HNPPC] and sCRC); the source of controls (included hospital-based study [HB], population-based study, and family-based study); genotyping method; sample size (numbers of cases/controls); genotypes; and the Hardy–Weinberg equilibrium (HWE) in the controls. If these two authors could not reach a consensus, the third author (YW) was consulted to resolve the dispute by discussion.

Statistical analysis
The distribution of genotypes in controls was calculated for departure from HWE by an online test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The crude ORs with their 95% CIs were used to determine the strength of correlation between CCND1 rs9344 G>A polymorphism and CRC risk. Heterogeneity assumption was assessed by the chi-square-based Q-test and F test. F > 0.10 indicates statistical heterogeneity among studies;22 so the pooled ORs and CIs were measured by the random-effects model (the DerSimioan and Laird method).23 Otherwise, the fixed-effects model (the Mantel–Haenszel method) was used.24 In order to check the ethnicity and the type of CRC effects, subgroup analyses were performed. Moreover, one-way sensitivity analysis was performed. Publication bias was tested by visual inspection of funnel plots and formally determined by Begg’ adjusted rank correlation test and Egger’ linear regression test.25 All statistical calculations were conducted with STATA version 12.0 (Stata Corporation, College Station, TX, USA). All P-values were two-sided, and P < 0.05 was defined as statistically significant.

Results

Characteristics
A total of 198 relevant publications were retrieved. There were several subgroups in certain publications,15,16,26 and we treated them separately. We listed the major screening process in Figure 1. Finally, there were 28 eligible studies included in the pooled analysis.12–18,26–42 There were 9 studies conducted in Asians,12,13,15,18,27,30,33,37,38 16 studies conducted in Caucasians,14–17,26,28,32,34,36,38–41 and 3 studies conducted in mixed populations.29,31,42 Of these articles, 22 investigated sCRC,12–18,26–38 and 6 investigated HNPPC.16,26,39,42 And the detailed characteristics of the included studies12–18,26–42 and the distribution of the CCND1 rs9344 G>A polymorphism as well as alleles are listed in Tables 1 and 2, respectively.
Quantitative synthesis
In total, 28 eligible studies with 5,784 CRC cases and 7,858 controls were included in our meta-analysis. Overall, the CCND1 rs9344 G>A polymorphism was associated with the overall CRC risk in four genetic models (A vs G: OR, 1.12; 95% CI: 1.03–1.21, \( P = 0.005 \); AA vs GG: OR, 1.25; 95% CI: 1.06–1.48, \( P = 0.008 \); AA+GA vs GG: OR, 1.18; 95% CI: 1.05–1.33, \( P = 0.007 \); AA vs GA+GG: OR, 1.13; 95% CI: 1.05–1.28, \( P = 0.042 \); Table 3 and Figure 2). In a subgroup analysis by CRC type, the CCND1 rs9344 G>A polymorphism was associated with an increased risk of sCRC in three genetic models (A vs G: OR, 1.13; 95% CI: 1.04–1.23, \( P = 0.004 \); AA vs GG: OR, 1.28; 95% CI: 1.07–1.54, \( P = 0.008 \); AA+GA vs GG: OR, 1.20; 95% CI: 1.06–1.36, \( P = 0.004 \); Table 3 and Figure 2), but not of HNPCC. In a subgroup analysis by ethnicity, an increased CRC risk was found among Caucasians in two genetic models (A vs G: OR, 1.11; 95% CI: 1.00–1.23, \( P = 0.049 \); AA+GA vs GG: OR, 1.16; 95% CI: 1.01–1.33, \( P = 0.041 \); Table 3 and Figure 3), and among Asians in one genetic model (A vs G: OR, 1.17; 95% CI: 1.00–1.36, \( P = 0.048 \); Table 3 and Figure 3), but not mixed populations.

Tests for publication bias, sensitivity analyses, and heterogeneity
Begg’s funnel plot and Egger’s linear regression test were harnessed to examine potential publication bias. As shown in Figure 4, no significant publication bias was detected in our study (Begg’s test \( P = 0.514 \); Egger’s test \( P = 0.259 \)). Influence of an individual study on the pooled ORs and CIs was also determined by omitting it in turn and repeating the meta-analysis. The results indicated that no individual study significantly altered the pooled ORs and CIs (Figure 5).

As shown in Table 3, there was significant heterogeneity in all genetic models. Because ethnicity, the type of CRC, and source of controls can affect the heterogeneity, subgroup analyses were conducted. Results showed that Asians, Caucasians, population-based study, HB study, and sCRC subgroups may contribute to the major source of heterogeneity.
Table 2 Distribution of CCND1 rs9344 G>A polymorphism genotypes and alleles

| Study         | Year | Case | Control | Case | Control | HWE |
|---------------|------|------|---------|------|---------|-----|
| Govatati et al | 2014 | 54   | GG      | 19   | 32      | 175 |
| Sameer et al  | 2013 | 9    | GA      | 20   | 15      | 18  |
| Jelonek et al | 2010 | 10   | AA      | 10   | 10      | 18  |
| Yaylim-Eraltan et al | 2010 | 9    | GG      | 10   | 10      | 18  |
| Kanaan et al  | 2010 | 10   | GA      | 10   | 10      | 18  |
| Liu et al     | 2010 | 9    | AA      | 10   | 10      | 18  |
| Forones et al | 2008 | 10   | GG      | 10   | 10      | 18  |
| Probst-Hensch et al | 2006 | 20   | GG      | 20   | 20      | 18  |
| Schernhammer et al | 2006 | 20   | GG      | 20   | 20      | 18  |
| Le Marchand et al | 2003 | 20   | GG      | 20   | 20      | 18  |
| Porter et al  | 2002 | 20   | GG      | 20   | 20      | 18  |
| Bala and Peltomaki | 2001 | 20   | GG      | 20   | 20      | 18  |
| King et al    | 2001 | 20   | GG      | 20   | 20      | 18  |
| McKay et al   | 2000 | 20   | GG      | 20   | 20      | 18  |
| Kong et al    | 2002 | 20   | GG      | 20   | 20      | 18  |

Abbreviation: HWE, Hardy-Weinberg equilibrium.
Table 3 Meta-analysis of the CCND1 rs9344 G→A polymorphism and CRC risk

| Group               | No of study | A vs G | OR (95% CI) | P-value (Q-test) | A vs GA-GG | OR (95% CI) | P-value (Q-test) | A vs GG | OR (95% CI) | P-value (Q-test) |
|---------------------|-------------|--------|-------------|-----------------|------------|-------------|-----------------|---------|-------------|-----------------|
| Ethnicity           |             |        |             |                 |            |             |                 |         |             |                 |
| Asians              | 9           | 1.17 (1.00–1.36) | 0.048 | 0.004 | 1.28 (1.07–1.54) | 0.002 | 1.38 (1.14–1.68) | 0.001 | 1.29 (1.07–1.56) | 0.001 |
| Caucasians          | 16          | 1.11 (1.00–1.23) | 0.049 | 0.005 | 1.23 (1.00–1.53) | 0.005 | 1.16 (1.01–1.33) | 0.041 | 1.20 (1.06–1.34) | 0.045 |
| Mixed               | 3           | 1.01 (0.97–1.06) | 0.235 | 0.125 | 1.00 (0.98–1.04) | 1.13 (1.05–1.26) | 0.004 | 1.13 (1.05–1.26) | 0.004 |
| Type of CRC         |             |        |             |                 |            |             |                 |         |             |                 |
| sCRC                | 22          | 1.13 (1.04–1.23) | 0.004 | 0.002 | 1.28 (1.07–1.54) | 0.002 | 1.38 (1.14–1.68) | 0.001 | 1.29 (1.07–1.56) | 0.001 |
| scCRC               | 11          | 1.19 (1.00–1.30) | 0.014 | 0.001 | 1.20 (1.06–1.34) | 0.001 | 1.17 (1.05–1.31) | 0.045 | 1.13 (1.00–1.28) | 0.004 |
| HNPPC               | 6           | 1.06 (0.96–1.16) | 0.106 | 0.120 | 0.97 (0.94–1.00) | 0.035 | 0.98 (0.95–1.02) | 0.035 | 0.98 (0.95–1.02) | 0.035 |
| FB                  | 15          | 1.09 (0.99–1.21) | 0.054 | 0.005 | 1.21 (1.07–1.36) | 0.002 | 1.20 (1.07–1.36) | 0.002 | 1.20 (1.07–1.36) | 0.002 |
| FB                  | 2           | 0.80 (0.64–1.06) | 0.120 | 0.120 | 0.90 (0.74–1.09) | 0.106 | 0.90 (0.74–1.09) | 0.106 | 0.90 (0.74–1.09) | 0.106 |

Note: Statistically significant values are shown in bold. CI, confidence interval; FB, family-based study; HB, hospital-based study; HNPPC, hereditary nonpolyposis colorectal cancer; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; PB, population-based.

Discussion

CCND1 may act as an important regulator in the evolution of malignancy by influencing cell proliferation, differentiation, and apoptosis. It has been reported that the G1–S transition of the cell cycle is controlled by sequential activation of cyclin/cyclin-dependent kinase (CDK) complexes.44 The CCND1, a vital cell cycle regulatory protein, regulates transition of G1–S phase during cell division. High activity of CCND1 leads to premature cell passage through the G1–S transition, resulting in proliferation of unrepaired DNA damage and genetic errors, thus leading to selective advantage for abnormal cell propagation.45 Previous studies indicated that CCND1 was overexpressed in a number of malignancies.6–46 Owing to these important roles in carcinogenesis, polymorphisms of CCND1 may be implicated in accelerating the development and/or progression of CRC.

Of late, numerous epidemiologic investigations focused on the relationship of the CCND1 polymorphism with CRC risk.12–18,26–42 The most prevalent CCND1 gene polymorphism, rs9344 G>A, has been most widely explored. High activity of CCND1 is common in a lot of human tumors.57,48 Several case–control studies have reported a positive signal of the CCND1 rs9344 G>A polymorphism with the risk of CRC,10–16 however, others have reported negative signal.17,18 Because of conflicting results and the insufficient sample size of individual studies, the final decision was far from certain. Because meta-analysis is a powerful way for pooling the results of all included studies with a more power, it can get more robust results than an individual study.49 Our findings showed that the presence of the CCND1 rs9344 A allele, which elevate CCND1 activity,8,9 might confer the susceptibility to CRC. In addition, subgroup analyses were performed regarding ethnicity and the type of CRC for this polymorphism. CCND1 rs9344 G>A polymorphism increased the risk of CRC among Asians, Caucasians, and sCRC. Results of the current meta-analysis indicated the influence of the CCND1 rs9344 G>A polymorphism and diversity on the type of CRC. However, our results should be interpreted with very caution. For HNPPC, only six studies with small sample sizes were included in this group, which may restrict the statistical power to obtain a final decision.16,26,39,42 When stratified by ethnicity, the CCND1 rs9344 G>A polymorphism was associated with CRC risk in both Asians and Caucasians. Additionally, in other genetic models, a borderline risk of CRC was also observed in these two ethnicities. Results of several previous meta-analyses showed that the CCND1 rs9344 G>A polymorphism might be a risk factor for CRC, especially in the subgroups of sCRC and Caucasians.19–21 Our results were very analogous to these...
pooled analyses. In addition, we also found that the CCND1 rs9344 G>A polymorphism might be a risk factor for CRC risk in Asians.

The CCND1 rs9344 G allele may provide an optimal splice donor site and produce a full transcript for CCND1 (transcript a), whereas the CCND1 rs9344 A allele results in a truncated transcript (transcript b). The well-described transcript (transcript a) interacts with and activates the downstream molecules, such as G1 CDK, CDK4, and CDK6. Then, the CCND1–CDK complex phosphorylates and inhibits the retinoblastoma tumor suppressor, which is necessary for the G1–S transition. However, a truncated transcript (transcript b) encodes the protein short of the point estimation by sequential testing (PEST) region in the C-terminal domain and decreases phosphorylation ability of retinoblastoma. On the other hand, the transcript b has a longer half-life than transcript a, which may result in an overexpression of CCND1. Subsequently, the CCND1 rs9344 G→A substitution could lead to facilitation of cell proliferation and increase the susceptibility of malignancy. The findings of our meta-analysis were consistent with the conclusion of previous functional studies mentioned earlier. The epidemiologic investigations provided evidence suggesting that CRC carcinogenesis may be multiple steps that involve both individual’s genetic and environmental factors. In the future, larger epidemiologic studies with a well-designed methodology are needed to

| Study ID | OR (95% CI) | % weight |
|----------|-------------|----------|
| sCRC     |             |          |
| Govatati et al\(^\text{12}\) (2014) | 1.80 (1.14, 2.85) | 2.12 |
| Sameer et al\(^\text{17}\) (2013) | 1.37 (0.99, 1.91) | 3.27 |
| Jelonek et al\(^\text{17}\) (2010) | 0.82 (0.52, 1.29) | 2.15 |
| Yaylim-Eraltan et al\(^\text{19}\) (2010) | 1.50 (0.96, 2.37) | 2.16 |
| Kanaan et al\(^\text{19}\) (2010) | 1.01 (0.66, 1.56) | 2.33 |
| Liu et al\(^\text{20}\) (2010) | 1.08 (0.91, 1.29) | 5.59 |
| Forones et al\(^\text{20}\) (2008) | 1.01 (0.70, 1.44) | 2.96 |
| Tan et al\(^\text{20}\) (2008) | 0.99 (0.84, 1.18) | 5.69 |
| Grunhage et al\(^\text{20}\) (2008) | 0.98 (0.70, 1.38) | 3.16 |
| Jing et al\(^\text{20}\) (2008) | 1.37 (0.97, 1.92) | 3.17 |
| Josifovski et al\(^\text{20}\) (2007) | 1.15 (0.84, 1.58) | 3.44 |
| Probst-Hensch et al\(^\text{21}\) (2006) | 1.02 (0.85, 1.22) | 5.44 |
| Schernhammer et al\(^\text{20}\) (2006) | 0.97 (0.85, 1.12) | 6.23 |
| Jiang et al\(^\text{20}\) (2006) | 1.35 (1.07, 1.71) | 4.60 |
| Hong et al\(^\text{20}\) (2005) | 0.66 (0.47, 0.92) | 3.21 |
| Grieu et al\(^\text{20}\) (2003) | 0.97 (0.80, 1.18) | 5.27 |
| Le Marchand et al\(^\text{20}\) (2003) | 1.58 (0.99, 2.52) | 2.06 |
| Le Marchand et al\(^\text{20}\) (2003) | 1.06 (0.85, 1.31) | 4.89 |
| Le Marchand et al\(^\text{20}\) (2003) | 1.45 (1.05, 2.01) | 3.35 |
| Porter et al\(^\text{20}\) (2002) | 1.39 (1.05, 1.84) | 3.88 |
| Kong et al\(^\text{20}\) (2001) | 1.58 (1.15, 2.17) | 3.41 |
| McKay et al\(^\text{20}\) (2000) | 1.20 (0.81, 1.78) | 2.62 |
| Subtotal (\(I^2=52.4\%, P=0.002\)) | 1.13 (1.04, 1.23) | 81.01 |

| HNPCC |             |          |
|-------|-------------|----------|
| Talseth et al\(^\text{20}\) (2008) | 1.33 (0.97, 1.82) | 3.44 |
| Grunhage et al\(^\text{20}\) (2008) | 1.40 (0.99, 1.98) | 3.12 |
| Kruger et al\(^\text{20}\) (2006) | 0.87 (0.69, 1.11) | 4.52 |
| Porter et al\(^\text{20}\) (2002) | 1.21 (0.85, 1.73) | 3.02 |
| Bala and Peltomaki\(^\text{20}\) (2001) | 0.76 (0.56, 1.03) | 3.52 |
| Kong et al\(^\text{20}\) (2000) | 1.01 (0.55, 1.86) | 1.38 |
| Subtotal (\(I^2=58.4\%, P=0.035\)) | 1.06 (0.86, 1.32) | 18.99 |
| Overall (\(I^2=52.3\%, P=0.001\)) | 1.12 (1.03, 1.21) | 100 |

Figure 2 Meta-analysis with a random-effects model in the different type for the association between CCND1 rs9344 G>A polymorphism and CRC risk (A vs G genetic model).

Note: Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; OR, odds ratio; sCRC, sporadic colorectal cancer.
confirm or refute these associations. Results of our pooled analysis may prompt further clinic investigation of diagnosis and prevention strategies.

There were some merits in this meta-analysis. First, the current meta-analysis was the most extensively study which explored the relationship of the CCND1 rs9344 G>A polymorphism with CRC susceptibility. Second, our results first confirmed that the CCND1 rs9344 G>A polymorphism was associated with CRC susceptibility among Asians.

**Limitations**

There were some limitations of our study. First, in some included studies, controls were selected from family member...

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**Table 1** Study ID and OR (95% CI) % weight

| Study ID                  | OR (95% CI) | % weight |
|--------------------------|-------------|----------|
| Asians                   |             |          |
| Govatati et al<sup>12</sup> (2014) | 1.80 (1.14, 2.85) | 2.12     |
| Sameer et al<sup>17</sup> (2013) | 1.37 (0.99, 1.91) | 3.27     |
| Liu et al<sup>16</sup> (2010) | 1.08 (0.91, 1.29) | 5.59     |
| Jing et al<sup>18</sup> (2008) | 1.37 (0.97, 1.92) | 3.17     |
| Probst-Hensch et al<sup>21</sup> (2006) | 1.02 (0.85, 1.22) | 5.44     |
| Jiang et al<sup>13</sup> (2006) | 1.35 (1.07, 1.71) | 4.60     |
| Hong et al<sup>16</sup> (2005) | 0.68 (0.47, 0.92) | 3.21     |
| Le Marchand et al<sup>23</sup> (2003) | 1.58 (0.99, 2.52) | 2.96     |
| Le Marchand et al<sup>23</sup> (2003) | 1.06 (0.85, 1.31) | 4.89     |
| Subtotal (P=64.7%, P=0.004) | 1.17 (1.00, 1.36) | 34.35   |
| Caucasians               |             |          |
| Jelonek et al<sup>17</sup> (2010) | 0.82 (0.52, 1.29) | 2.15     |
| Yarim-Erlatan et al<sup>19</sup> (2010) | 1.50 (0.96, 2.37) | 2.16     |
| Tan et al<sup>21</sup> (2008) | 0.99 (0.84, 1.18) | 5.69     |
| Talseth et al<sup>23</sup> (2008) | 1.33 (0.97, 1.82) | 3.44     |
| Grunhage et al<sup>21</sup> (2008) | 1.40 (0.99, 1.98) | 3.12     |
| Grunhage et al<sup>21</sup> (2008) | 0.98 (0.70, 1.38) | 3.16     |
| Josifovski et al<sup>24</sup> (2007) | 1.15 (0.84, 1.58) | 3.44     |
| Kruger et al<sup>26</sup> (2006) | 0.87 (0.69, 1.11) | 4.52     |
| Schernhammer et al<sup>24</sup> (2006) | 0.97 (0.85, 1.12) | 6.23     |
| Grieu et al<sup>26</sup> (2003) | 0.97 (0.80, 1.18) | 5.27     |
| Le Marchand et al<sup>23</sup> (2003) | 1.45 (1.05, 2.01) | 3.35     |
| Porter et al<sup>26</sup> (2002) | 1.21 (0.85, 1.73) | 3.02     |
| Porter et al<sup>26</sup> (2002) | 1.39 (1.05, 1.84) | 3.88     |
| Bala and Peltomaki<sup>21</sup> (2001) | 0.76 (0.56, 1.03) | 3.52     |
| Kong et al<sup>21</sup> (2001) | 1.58 (1.15, 2.17) | 3.41     |
| McKay et al<sup>26</sup> (2000) | 1.20 (0.81, 1.78) | 2.62     |
| Subtotal (P=54.0%, P=0.005) | 1.11 (1.00, 1.23) | 58.98   |
| Mixed                    |             |          |
| Kanaan et al<sup>13</sup> (2010) | 1.01 (0.66, 1.56) | 2.33     |
| Forones et al<sup>11</sup> (2008) | 1.01 (0.70, 1.44) | 2.96     |
| Kong et al<sup>12</sup> (2000) | 1.01 (0.55, 1.86) | 1.38     |
| Subtotal (P=0.0%, P=1.000) | 1.01 (0.79, 1.30) | 6.67     |
| Overall                  | 1.12 (1.03, 1.21) | 100      |

**Figure 3** Meta-analysis with a random–effects model in different races for the association between the CCND1 rs9344 G>A polymorphism and CRC risk (A vs G genetic model).

**Note:** Weights are from random-effects analysis.

**Abbreviations:** CI, confidence interval; CRC, colorectal cancer; OR, odds ratio.

**Figure 4** Begg’s funnel plot of meta-analysis of the relationship between the CCND1 rs9344 G>A polymorphism and CRC risk (AA vs GA+GG genetic model).

**Abbreviations:** CRC, colorectal cancer; OR, odds ratio; SE, standard error.
and non-cancer hospital patients, which might result in misclassification bias. Second, large heterogeneity was observed in our meta-analysis, which means our findings should be interpreted with caution. Finally, our findings were based on unadjusted ORs and CIs, while a more precise measurement should be adjusted by multiple risk factors, such as family history, smoking status, drinking, diabetes, body mass index, etc.

**Conclusion**

In summary, this meta-analysis suggests that the **CCND1** rs9344 G>A polymorphism is correlated with increased risk of CRC. Moreover, these relationships were different across different cancer types of CRC, suggesting that large sample and well-designed epidemiologic studies are warranted to confirm or refute our findings.

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**Disclosure**

The authors report no conflicts of interest in this work.

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