Meta-analysis of the association of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer


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The aim of this study is to comprehensively evaluate the associations of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer (CRC). We searched the English and Chinese databases and recruited case-control studies based on strict inclusion and exclusion criteria. The statistical analysis was performed by the Comprehensive Meta-analysis 2.0 (CMA 2.0) software and this initially identified 251 studies. We then recruited 10 English studies to this meta-analysis detailed review which includes 9,415 CRC patients and 14,179 healthy controls. Our results demonstrated that IGFBP3 rs2854746 C>G polymorphism increases susceptibility to the CRC (allele model: OR=1.167, 95% CI=1.095~1.244, p<0.001 and to the dominant gene model: OR=1.226, 95% CI=1.113~1.350, p<0.001); but IGFBP3 rs2854744 A>C has no significant association with the CRC susceptibility (allele model: OR=0.970, 95% CI=0.932~1.010, p=0.138; dominant gene model: OR=0.995, 95% CI=0.936~1.057, p=0.874). Also, IGF1 rs35767 C>T polymorphism decreases susceptibility to CRC (allele model: OR=0.785, 95% CI=0.726~0.850, p<0.001 and also the dominant model: OR=0.730, 95% CI=0.661~0.806, p<0.001). However, IGFBP3 rs2854746 C>G is considered the susceptible CRC polymorphism and IGF1 rs35767 C>T is CRC protective.

Key words: IGFBP3, IGF1, rs2854746 C>G, rs35767 C>T, polymorphism, colorectal cancer

Both colon and colorectal cancer (CRC) originate from uncontrolled cell proliferation in the gastrointestinal epithelial cell lining [1]. CRC is the third most common cancer worldwide with a global incidence exceeding 1.2 million new cases and 600,000 deaths per year, and the mortality rate is lower in men than in women [2, 3]. The progression of CRC from benign adenoma to malignant adenocarcinoma and distant metastasis, normally takes a long time and CRC can therefore be cured if detected at an early stage. However, two thirds of patients with CRCs are diagnosed at a more advanced stage because early-stage disease is mostly asymptomatic [4]. Therefore, screening and early diagnosis are more preferable to efficiently relieving the burden of disease [5]. Although the etiopathogenesis of CRC is adventitious, epigenetic alterations of both proto-oncogenes and tumor suppressor genes are critical in tumorigenesis mechanisms [6]. As decisive factors in proliferation and apoptosis, the insulin-like growth factor (IGF) axis and functional insulin deregulation are considered the potential mechanisms explaining colorectal carcinogenesis [7].

IGF1, a protein encoded by the IGF1 gene located on chromosome 12 [8], exerts biological effects through activating the insulin-like growth factor type 1 receptor (IGF-1R), but the relationship between expressions of IGF1 and IGF-1R and CRC clinical-pathological factors remains unclear [9]. IGF1 and members of the IGF-binding protein family (IGFBPs) are essential for cell cycle regulation [10]. IGF1, as a peptide growth factor, can improve cell proliferation and restrain apoptosis and is also regulated by the insulin-like growth factor binding protein IGFBP3 [11]. Extant studies show that IGF1, IGFBP3 and insulin significantly influence the pathogenesis of colon cancer through regulating cell growth and proliferation [12, 13]. Moreover, the insulin level, IGF1 level, IGF1/IGFBP3 ratio and reduction of IGFBP3 may be related to the initiation of CRC, but not to the progression and outcome of the disease [12]. The IGF1 gene comprises a highly conservative sequence with 6 exons, which give rise to heterogeneous mRNA transcripts by combining multiple transcription initiation sites and alternative splicing [14]. The IGFBP3 gene, on human chromo-
some 7, is integrated in four protein-coding exons and a 5th exon in the 3’ untranslated region [15]. IGFBP3 acts as a hypoxia-inducible gene and it regulates a series of cellular processes, including senescence, cell proliferation, epithelial-mesenchymal transition and apoptosis [16]. The activities of IGF-1 are controlled by interaction of several high-affinity IGFBPs; especially IGFBP3 which directly carries IGF-1 to target tissues, prevents it from proteolytic degradation and regulates its interaction with IGF-1R. Its expression is negatively related to IGF-1 expression [17, 18]. IGF1 and IGFBP3 gene polymorphisms may affect circulation levels of IGF1 and IGFBP3, and high IGF1 level but low IGFBP3 level contributes to increased cancer risk [7, 19]. In addition, IGFBP3 has an effect in its own IGF-independent apoptosis through mediation of a specific cell surface receptor [20]. These findings suggest that genetic variations in the IGF1 and the IGFBP3 genes play important roles in colorectal tumorigenesis [21, 22]. However, previous studies indicated that polymorphic variations in IGF1 and IGFBP3 genes may have no association with the CRC risk [11, 23, 24]. This present study therefore investigates the relationship of IGF1 and IGFBP3 polymorphisms with colorectal cancer susceptibility.

### Materials and methods

**Search methods.** We searched PubMed (1996–Aug. 2017), Cochrane Library (CENTRAL, 2017), Embase (1986–Aug. 2017), CNKI (1994–Aug. 2017) and Wanfang database (1986–Aug. 2017), following search terms: “Colorectal Neoplasms” or “Colorectal Neoplasm” or “Colorectal Tumor” or “Colorectal Carcinoma” or “Colorectal Cancer” or “Colorectal Cancer” and “Insulin-Like Growth Factor Binding Protein 3” or “IGFBP-3” or “IGF-Binding Protein 3” or “IGF Binding Protein 3” or “Protein 3, IGF-Binding” and “Polymorphism, Genetic” or “Genetic Polymorphism” or “Polymorphism, Genetic” and “IGF1 protein, human”. Then we manually searched the reference lists of the retrieved articles and reviews in other relevant studies.

**Inclusion and exclusion criteria.** Studies were based on the following inclusion criteria: (1) all studies had to be case-controlled, with participants divided into CRC and non-CRC groups; (2) the research topic was associated with the IGFBP3 and IGF1 gene polymorphism and susceptibility to CRC; (3) the outcome index ensured the studies provided the information for IGFBP3 rs2854746 C>G, rs2854744 A>C and IGF1 rs35767 C>T. The exclusion criteria were: (1) summaries and abstracts only; (2) duplicated studies and (3) insufficient statistics. Inclusion was discussed until consensus was reached.

**Data extraction.** Two independent investigators extracted the data from eligible studies. Two authors reviewed all articles that suited inclusion criteria. The information was collected as follows: surname and initials of the first author, year of publication, source country, language of publication, cases, demographic variables of the subjects, study designs, diagnostic methods, single nucleotide polymorphisms (SNPs), and genotype frequencies; disagreement was solved by a third investigator.

**Statistical analysis.** Data analysis was performed by Comprehensive Meta-analysis 2.0 (CMA 2.0; Biostatic Inc., Englewood, New Jersey, USA). Hardy-Weinberg equilibrium (HWE) was assessed by χ² test in the control group of each study. Odds ratio (OR) and 95% confidence intervals (95% CI) for CRC were calculated by comparing differences in allele and genotype frequency of TLR4 rs4986790A>G and rs4986791 C>T polymorphisms. The significance of overall effect sizes was evaluated by Z test [25]. Forest plots were applied to reflect the comparisons of ORs and 95% CI between the case study and controls. The heterogeneity between included trials was estimated by the Cochran’s Q-statistic (p<0.05 was considered significant) and also the I² test (0%, no heterogeneity; 100%, maximal heterogeneity) [25, 26]. The fixed-effect model was applied to calculate parameters when heterogeneity was not an issue; otherwise the random effect model was used [27]. Meta-regression univariate analysis was applied to identify potential sources of heterogeneity and the Monte Carlo simulation for further confirmation [28–30]. Sensitivity analysis evaluated whether the removal of a single study would influence the overall outcome. The Egger’s linear regression test, funnel plot and classic fail-safe-N analyzed publication bias [31–33]. All tests were two-sided, and p<0.05 indicated statistical significance.

### Results

**Selection of eligible studies.** Our search identified 251 relative studies. After excluding duplicates (n=32), letters, reviews and meta-analysis (n=48), non-human studies (n=21) and studies irrelevant to research topics (n=70), we reviewed 80 full-text articles. Through detailed evaluation, we further excluded 67 studies (14 uncontrolled case studies, 18 studies irrelevant to IGFBP3 or IGF1, 35 studies irrelevant to CRC) and 3 studies with irrelevant data. Finally, 10 eligible case-control studies from 2005–2012 [7, 13, 22, 23, 34–39] were incorporated in the study. They comprised 9,415 CRC patients and 14,179 healthy controls, and the sample size in each study ranged from 414 to 5,271. The flow chart of selection of eligible studies is shown in Figure 1. Eight studies were conducted in Caucasians and 2 in Asians. Polymerase chain reaction with the restriction fragment length polymorphism (PCR–RFLP) and TaqMan assay were applied for detection of SNP. In most eligible studies, the genotype distributions of studied loci were in accordance with the HWE (all p>0.05); except two studies with IGF1 rs35767 C>T [23, 36] and one study with IGFBP3 rs2854744 A>C [34]. The IGFBP3 and IGF1 gene loci-related information is summarized in Table 1.
Table 1. The IGFBP3 and IGF1 variants that have ever been reported in colorectal cancer and characteristics of studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Genes</th>
<th>Study design</th>
<th>Source of controls</th>
<th>Genotype method</th>
<th>Sample size (case/control)</th>
<th>Adjusted factors</th>
<th>HWE</th>
<th>CASP score</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2854746 (C&gt;G)</td>
<td>Ollberding NJ [36]</td>
<td>2012</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>1954/2587</td>
<td>1,2,3,4,5,6</td>
<td>0.100</td>
<td>10</td>
</tr>
<tr>
<td>rs2854746 (C&gt;G)</td>
<td>Feik E [13]</td>
<td>2010</td>
<td>Austria</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>178/1795</td>
<td>1,2,3,4,5,6</td>
<td>0.450</td>
<td>9</td>
</tr>
<tr>
<td>rs2854746 (C&gt;G)</td>
<td>Xiang H [22]</td>
<td>2009</td>
<td>China</td>
<td>Asians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>202/212</td>
<td>1,2,3,4,5,6</td>
<td>0.717</td>
<td>8</td>
</tr>
<tr>
<td>rs2854746 (C&gt;G)</td>
<td>Pechlivanis S [23]</td>
<td>2007</td>
<td>Germany</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>661/607</td>
<td>1,2,3,4,5,6</td>
<td>0.392</td>
<td>9</td>
</tr>
<tr>
<td>rs2854746 (C&gt;G)</td>
<td>Morimoto LM [35]</td>
<td>2005</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>782/503</td>
<td>1,2,3,4,5,6</td>
<td>0.098</td>
<td>8</td>
</tr>
<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Ollberding NJ [36]</td>
<td>2012</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>1954/2587</td>
<td>1,2,3,4,5,6</td>
<td>0.100</td>
<td>10</td>
</tr>
<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Keku TO [7]</td>
<td>2012</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>552/873</td>
<td>1,2,3,4,5,6</td>
<td>0.255</td>
<td>9</td>
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<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Feik E [13]</td>
<td>2010</td>
<td>Austria</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>178/1795</td>
<td>1,2,3,4,5,6</td>
<td>0.450</td>
<td>9</td>
</tr>
<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Xiang H [22]</td>
<td>2009</td>
<td>China</td>
<td>Asians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>202/212</td>
<td>1,2,3,4,5,6</td>
<td>0.717</td>
<td>8</td>
</tr>
<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Pechlivanis S [23]</td>
<td>2007</td>
<td>Germany</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>661/607</td>
<td>1,2,3,4,5,6</td>
<td>0.392</td>
<td>9</td>
</tr>
<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Slattery ML [38]</td>
<td>2006</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>2371/2972</td>
<td>1,2,3,4,5,6</td>
<td>0.844</td>
<td>8</td>
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<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Samowitz WS [37]</td>
<td>2006</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>1788/1891</td>
<td>1,2,3,4,5,6</td>
<td>0.325</td>
<td>9</td>
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<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Wong HL [39]</td>
<td>2005</td>
<td>Singapore</td>
<td>Asians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>290/873</td>
<td>1,2,3,4,5,6</td>
<td>0.112</td>
<td>8</td>
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<tr>
<td>rs2854744 (A&gt;C)</td>
<td>Le Marchand L [34]</td>
<td>2005</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGFBP3</td>
<td>Case-Control</td>
<td>PB</td>
<td>PCR-RFLP</td>
<td>2298/2749</td>
<td>1,2,3,4,5,6</td>
<td>0.817</td>
<td>9</td>
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<tr>
<td>rs35767 (C&gt;T)</td>
<td>Ollberding NJ [36]</td>
<td>2012</td>
<td>USA</td>
<td>Caucasians</td>
<td>IGF1</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>1954/2587</td>
<td>1,2,3,4,5,6</td>
<td>0.100</td>
<td>10</td>
</tr>
<tr>
<td>rs35767 (C&gt;T)</td>
<td>Feik E [13]</td>
<td>2010</td>
<td>Austria</td>
<td>Caucasians</td>
<td>IGF1</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>178/1795</td>
<td>1,2,3,4,5,6</td>
<td>0.450</td>
<td>9</td>
</tr>
<tr>
<td>rs35767 (C&gt;T)</td>
<td>Pechlivanis S [23]</td>
<td>2007</td>
<td>Germany</td>
<td>Caucasians</td>
<td>IGF1</td>
<td>Case-Control</td>
<td>PB</td>
<td>TaqMan</td>
<td>661/607</td>
<td>1,2,3,4,5,6</td>
<td>0.392</td>
<td>9</td>
</tr>
</tbody>
</table>

Notes: CASP, critical appraisal skill program; HWE, Hardy-Weinberg equilibrium; PB, population based; 1, Year; 2, Country; 3, Ethnicity; 4, Genotype method; 5, SNP; 6, Sample size.

Associations between IGFBP3 gene rs2854746 C>G polymorphism and CRC susceptibility. Five studies demonstrated the associations of IGFBP3 gene rs2854746 C>G with susceptibility to CRC. The random effect model was adopted because of observed heterogeneity in the allele model and dominant gene model (p<0.05). Results demonstrated that IGFBP3 gene rs2854746 C>G polymorphism increases susceptibility to CRC (allele model: OR=1.167, 95% CI=1.095~1.244, p<0.001; dominant gene model: OR=1.226, 95% CI=1.113~1.350, p<0.001) (Figures 2A, 2B, Table 2).
The subgroup analyses based on ethnicity determined that  
IGFBP3 gene rs2854746 C>G polymorphism may increase  
the CRC susceptibility among both Asians and Caucasians  
(Asians: allele model: OR=1.448, 95% CI=1.058–1.982,  
\( p=0.021 \); dominant model: OR=1.554, 95% CI=1.052–2.296,  
\( p=0.027 \); Caucasians: allele model: OR=1.156, 95% CI=1.083–1.234,  
\( p<0.001 \); allele model: OR=1.207, 95% CI=1.092–1.334,  
\( p<0.001 \)) (Figures 3A, B).

Table 2. Comparisons of genotype and allele frequencies between the case and the control groups.

<table>
<thead>
<tr>
<th>SNP</th>
<th>rs2854746 C&gt;G OR 95%CI p-value</th>
<th>rs2854744 A&gt;C OR 95%CI p-value</th>
<th>rs35767 C&gt;T OR 95%CI p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M allele vs. W allele (Allele model) Overall</td>
<td>1.167 1.095–1.244 ( &lt;0.001 )</td>
<td>0.97 0.932–1.010 0.138</td>
<td>0.785 0.726–0.850 ( &lt;0.001 )</td>
</tr>
<tr>
<td>WM + MM vs. WW (Dominant model) Overall</td>
<td>1.226 1.113–1.350 ( &lt;0.001 )</td>
<td>0.995 0.936–1.057 0.874</td>
<td>0.73 0.661–0.806 ( &lt;0.001 )</td>
</tr>
<tr>
<td>MM vs. WW (Homozygous model) Overall</td>
<td>1.3 1.150–1.470 ( &lt;0.001 )</td>
<td>0.957 0.880–1.036 0.227</td>
<td>0.721 0.594–0.876 0.001</td>
</tr>
<tr>
<td>MM vs. WM (Heterozygous model) Overall</td>
<td>0.891 0.795–0.999 0.048</td>
<td>0.963 0.816–1.136 0.656</td>
<td>1.155 0.947–1.408 0.115</td>
</tr>
<tr>
<td>MM vs. WW + WM (Recessive model) Overall</td>
<td>1.191 1.072–1.324 ( &lt;0.001 )</td>
<td>0.927 0.866–1.126 0.472</td>
<td>0.778 0.645–0.939 0.009</td>
</tr>
</tbody>
</table>

Notes: OR, odds ratio.

Figure 2. Forest plots for the association of  
IGFBP3 gene rs2854746 C>G and rs2854744 A>C polymorphism and  
IGF1 gene rs35767 C>T polymorphism with CRC susceptibility. Under allele mode and dominant model,  
IGFBP3 gene rs2854746 C>G and IGF1 gene rs35767 C>T polymorphism  
could increase the CRC susceptibility (all \( p<0.05 \), shown in A, B, E, F), while IGFBP3 gene rs2854744 A>C polymorphism had no significant influence  
on the susceptibility to CRC (all \( p>0.05 \), shown in C, D). The complete set of statistical data is in Supplementary Figure 1.
Associations between IGFBP3 gene rs2854744 A>C polymorphism and CRC susceptibility

Nine studies demonstrated association of IGFBP3 gene rs2854744 A>C with CRC susceptibility. The fixed effect model was adopted because no heterogeneity was observed in the allele model or dominant gene model (p>0.05). The results demonstrated that IGFBP3 gene rs2854744 A>C polymorphism had no significant influence on susceptibility to CRC (allele model: OR=0.970, 95% CI=0.932–1.010, p=0.138; dominant model: OR=0.995, 95% CI=0.936–1.057, p=0.874) (Figures 2C, 2D, Table 2). The subgroup analyses based on ethnicity established that IGFBP3 gene rs2854744 A>C polymorphism was unrelated to CRC susceptibility in both Caucasian and Asian subjects (p>0.05) (Figures 3C, D).

Associations between IGF1 gene rs35767 C>T polymorphism and CRC susceptibility

Three studies demonstrated the associations of IGF1 gene rs35767 C>T polymorphism with susceptibility to CRC. The random effect model was adopted because observed heterogeneity in the allele and dominant gene models (p<0.05). The results demonstrated that IGF1 gene rs35767 C>T polymorphism decreased the CRC susceptibility (allele model: OR=0.785, 95% CI=0.726–0.850, p<0.001 and dominant model: OR=0.730, 95% CI=0.661–0.806, p<0.001) (Figures 2E, 2F, Table 2). No subgroup analysis was made on ethnicity because eligible studies only included Caucasians.

Sensitivity analysis and publication bias. Sensitivity analysis indicated that the IGFBP3 gene rs2854746 C>G, rs2854744 A>C and IGF1 gene rs35767 C>T showed no significant influences on pooled ORs of CRC (Figure 4). Publication year, country, ethnicity, SNPs, genotype methods and sample size were not the main sources of heterogeneity or crucial factors in the overall size of the effect. This was indicated by the univariate meta-regression analysis (all p>0.05) (Figure 5). The shape of funnel plots of genotype differences in IGFBP3 gene rs2854746 C>G, rs2854744 A>C and IGF1 gene rs35767 C>T did not show any evidence of symmetry and the statistical results did not show publication bias. No existence of obvious publication bias was found by Classic fail-safe N and Egger’s linear regression test (all p>0.05) (Figure 6).

Discussion

We conducted this meta-analysis to investigate associations of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer; and we finally concluded that IGFBP3 rs2854746 C>G and IGF1 rs35767 C>T correlated with CRC. Specifically, IGFBP3 rs2854746 C>G is most likely
the susceptible CRC polymorphism and IGF1 rs35767 C>T may be the protective CRC polymorphism.

Our overall findings demonstrated that IGF1 rs35767 C>T polymorphism decreased the susceptibility to CRC while IGFBP3 rs2854746 C>G polymorphism increased CRC susceptibility. The IGF family is expected to have an essential role in regulating cell proliferation, apoptosis, and transformation [11]. IGF1, widely regarded as a circulating growth factor, is normally produced by the liver and participates in mediating body growth through growth hormone effects [40], but it is fatal for the normal development and growth of cell maintenance and homeostasis [9].

A previous study also showed that IGF1 is expressed locally in many tissues, including skeletal muscle, thus implying that paracrine and autocrine effects of local IGF1 are a major mechanism controlling tissue growth [41]. Moreover, IGF1, a peptide growth factor, stimulates cell division and inhibits apoptosis and its abnormal expression could therefore contribute to cancer development and metastasis; including in CRC [11, 42].

To regulate cellular growth and differentiation, the IGF system and apoptosis circulate IGF family growth factors which bind IGFBP proteins and IGF receptors 1 and 2 cell surface receptors [36]. IGFBP3 has inherent anti-proliferative and pro-apoptotic ability, and the circulating IGF1 and IGFBP3 concentrations and downstream signaling molecules may relate to CRC [43]. It has been reported that high levels of circulating IGF1 and/or low levels of IGFBP3 are associated with elevated CRC risk [44].

In addition, IGFBP-3 rs2854744 was recently reported to be related to IGFBP-3 concentration, and its C allele may lower IGFBP-3 concentration [11].

### Figure 4: Sensitivity analysis for the association of IGFBP3 gene rs2854746 C>G and rs2854744 A>C polymorphism and IGF1 gene rs35767 C>T polymorphism with CRC susceptibility.

Under allele mode and dominant model, the IGFBP3 gene rs2854746 C>G, rs2854744 A>C and IGF1 gene rs35767 C>T showed no significant influences on pooled ORs of CRC. The complete set of statistical data is shown in Supplementary Figure 3.
IGFBP3 AND IGF1 GENES POLYMORPHISMS WITH CRC

Figure 5. Meta-regression analysis for the association of IGFBP3 gene rs2854746 C>G and rs2854744 A>C polymorphism and IGF1 gene rs35767 C>T polymorphism with CRC susceptibility. Publication year, country, ethnicity, SNPs, genotype methods and sample size were not the main sources of heterogeneity or crucial factors in the overall size effect; as indicated in the univariate meta-regression analysis (all p>0.05).

IGFBP-3 can modulate the mitogenic and metabolic effects of IGFs encoded by the IGFBP-3 gene [16]. The IGFBP3 circulating level is significantly influenced by the IGFBP3 gene rs2854746 C>G located at position –202 (rs2854744, A.C) as a transcription start-site affecting promoter activity and rs35767 C>T is regarded as a non-synonymous substitution with the Gly32Ala (rs2854746, G.C) site providing high affinity IGF1 binding [45]. Rare variant alleles of the functional G2133C, rs2854746 polymorphisms have consistently been associated with decreased circulating levels of IGFBP3, thus suggesting that the exon 1 G2133C missense variant in IGFBP3 is critical in silencing its expression [7, 46]. This indicates that the IGFBP3rs2854746 SNP increases CRC risk by inhibiting the circulating level of IGFBP3. Previous studies support our findings by demonstrating that the exon 1 G2133C missense variant in IGFBP3 may be a susceptibility factor for CRC in an allele dose-responsive manner [22, 34]. IGFBP3 is the binding protein for IGF1 that decreases cancer risk by mediating the bioavailability of freely circulating IGF1. This stimulates apoptosis and reduces cell proliferation in an IGF1–independent manner [36].

There are several limitations in our meta-analysis. We had no access to original data from included studies and this limited further research into potential interactions. The fact that only one rs2854746 study for Asian ethnicity was included may cause bias. Moreover, differing language in published studies could also cause bias in the overall estimates.

Subgroup analyses based on ethnicity were then conducted to consider the influence of ethnicity on the associations of IGFBP3 gene rs2854746 C>G and IGF1 gene rs35767 C>T polymorphisms with CRC. These ethnicity-stratified analyses revealed the influence of ethnicity on associations.
between IGFBP3 gene and CRC risk. The subgroup analysis suggested that IGFBP3 gene rs2854746 C>G polymorphism increased susceptibility to CRC in both Asians and Caucasians. Moreover, no significant associations between IGFBP3 gene rs2854744 A>C polymorphism and CRC susceptibility were observed in either Asians or Caucasians.

In conclusion, our study demonstrates that IGFBP3 rs2854746 C>G is most likely the susceptible CRC polymorphism and IGF1 rs35767 C>T is the protective polymorphism in colorectal cancer.

Supplementary information is available in the online version of the paper.

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References


Meta-analysis of the association of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer


Supplemental Material

Supplementary Figure 1.

Supplementary Figure 2.
Supplementary Figure 3.

Supplementary Figure 4.