Int J Clin Exp Med 2015;8(3):3752-3760
www.ijcem.com /ISSN:1940-5901/IJCEM0005751

Original Article

Association between cytotoxic T-lymphocyte antigen-4 +49A/G polymorphism and colorectal cancer risk: a meta-analysis

Lei He, Tao Deng, He-Sheng Luo

Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan Hubei Province, China

Received January 10, 2015; Accepted February 25, 2015; Epub March 15, 2015; Published March 30, 2015

Abstract: The Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) gene has been implicated in the development of colorectal cancer (CRC). However, the results are inconsistent. In this study, we performed a meta-analysis to assess the associations between the CTLA-4 +49A/G polymorphism and risk of CRC. Relevant studies were identified using PubMed, Web of Science, CNKI and WanFang databases up to November 10, 2014. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association using the fixed or random effect model. A total of 8 case-control studies, including 1180 cases and 2110 controls, were included. Overall, a significant association between the CTLA-4 +49A/G polymorphism and CRC risk was found (dominant model: OR=1.63, 95% CI: 1.09-2.43; AG vs. AA: OR=1.69, 95% CI: 1.15-2.48). In the subgroup analysis by ethnicity, we observed a significant association in Asian descent (dominant model: OR=2.42, 95% CI: 1.40-4.16; AG vs. AA: OR=2.39, 95% CI: 1.52-3.76), but not among Europeans; when stratified by source of control, no significant association was detected in both population-based and hospital-based populations. This meta-analysis demonstrated that the CTLA-4 +49A/G polymorphism significantly increases the risk of CRC, especially for Asians.

Keywords: CTLA-4, polymorphism, colorectal cancer, meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death globally. Every year, more than 1.2 million patients are diagnosed with colorectal cancer, and more than 600000 die from the disease [1]. To date, the precise aetiology of CRC has not been completely elucidated. Epidemiological studies have demonstrated that some risk factors and interactions between genetic and environmental factors may play important roles in the pathogenesis of that cancer [2-4].

Cytotoxic T-lymphocyte antigen 4 (CTLA-4, also known as CD152), a member of the immunoglobulin superfamily that is expressed mainly on activated T cells, plays a critical role in the negative regulation of T-cell proliferation and activation [5]. In addition, CTLA-4 also induces Fas-independent apoptosis of activated T cells, which may inhibit immune function of T lymphocytes [6]. It has been suggested that, during the early stage of tumorigenesis, CTLA-4 may elevate the T-cell activation threshold, thereby attenuating the antitumor response and increasing susceptibility to cancer [7]. The CTLA-4 gene is located on chromosome 2q33, and it harbors four exons, three introns, and an upstream regulatory sequence [8]. Since the CTLA-4 gene product has inhibitory effects on the immune system, any variation in its expression or function may lead to the breakdown of the delicate homeostasis of this system. To date, several polymorphisms in the CTLA-4 gene have been identified [9, 10], such as +49A/G (rs231775) in exon 1, -318C/T (rs5742909), -1722T/C (rs733618), -1661A/G (rs4553808) in promoter region, and +6230G/A (known as CT60A/G, rs3087243) in the 3'-untranslated region. Among these, the +49A/G polymorphism is the most commonly studied one.

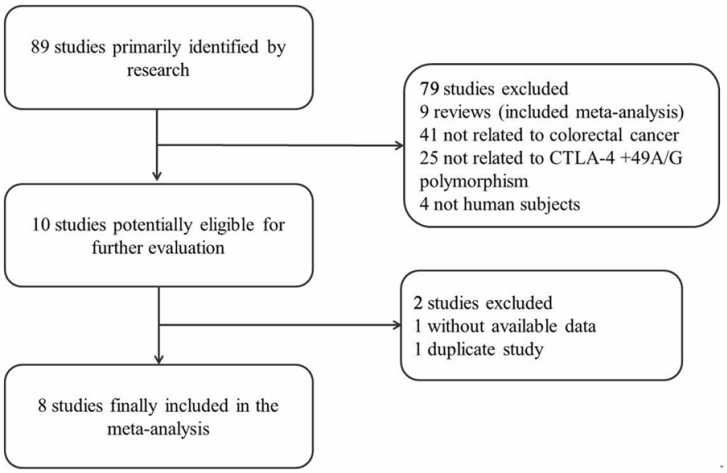

Figure 1. Flow chart showing study selection procedure.

In recent years, the +49A/G polymorphism has been extensively examined in association with risk of CRC [11-18]. However, the results are conflicting, some studies [12, 16, 17] supported that the polymorphism was a risk factor for CRC, whereas other studies [11, 13-15, 18] failed to detect the potential association. Hence, we conduct a meta-analysis to evaluate the association between CTLA-4 +49A/G polymorphism and CRC susceptibility.

Materials and methods

Search strategy

We searched the electronic literature PubMed, Web of Science, CNKI and WanFang databases for all relevant articles. The last search update was November 10, 2014, using the search terms: "Cytotoxic T-Lymphocyte Antigen-4 or CTLA-4" and "genetic polymorphism or polymorphisms or variant" and "colorectal cancer or CRC or colon cancer or rectal cancer or colorectal carcinoma or colon carcinoma or rectal carcinoma". The search was restricted to humans without language restrictions. Additional studies were identified by a hand search of references of original or review articles on this topic.

Inclusion criteria and exclusion criteria

Studies included in this meta-analysis have to meet the following criteria: (1) studies that evaluated the association between the CTLA-4 +49A/G polymorphism and colorectal cancer, (2) in a case-control study design, and (3) had detailed genotype frequency of cases and controls or could be calculated from the article text. While major exclusion criteria were: (1) case-only study, case reports, and review articles, (2) studies without the raw data of the CTLA-4 +49A/G genotype, and (3) repetitive publications.

Data extraction

For each study, the following data were extracted independently by two investigators (He L and Deng T): the first author's name, year of publication, country of origin, ethnicity, source of controls, genotype methods, number of cases and controls, and Hardy-Weinberg equilibrium (HWE) in controls (*P* value). The results were compared, and disagreements were discussed among all authors and resolved with consensus.

Statistical analysis

The risk of CRC associated with the CTLA-4 +49A/G polymorphism was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). Four different ORs were calculated: dominant model (AG+GG *vs.* AA), recessive model (GG *vs.* AG+AA), heterozygote comparison (AG *vs.* AA), and homozygote comparison (GG *vs.* AA). A χ^2-test-based Q statistic test was performed to assess the between-study heterogeneity [19]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P>0.05$) or $I^2<50\%$ indicated homogeneity across studies, the fixed effects model was used [20], otherwise, the random effects model was used [21]. HWE was evaluated for each study using χ^2 test. Then, we performed stratification analyses on ethnicity and source of controls. Analysis of sensitivity, after removing the study deviating from HWE, was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg's funnel plot and Egger's regression test [22, 23]. $P<0.05$ was considered statistically significant.

All analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package

Table 1. Characteristics of studies included in the meta-analysis

Study	Year	Country	Ethnicity	Source of control	Genotyping methods	Case			Control			P_{HWE}
						AA	AG	GG	AA	AG	GG	
Cozar [11]	2007	Spain	European	PB	TaqMan	46	44	6	78	77	21	0.766
Cui [12]	2013	China	Asian	PB	PCR-RFLP	9	46	73	53	68	84	0
Dilmec [13]	2008	Turkey	European	PB	PCR-RFLP	36	19	1	108	43	11	0.030
Fan [14]	2012	China	Asian	HB	PCR-RFLP	123	146	22	170	138	44	0.059
Hadinia [15]	2007	Iran	Asian	PB	PCR-RFLP	52	47	6	117	59	14	0.097
Li [16]	2011	China	Asian	HB	PCR-RFLP	8	120	120	42	167	171	0.898
Qi [17]	2010	China	Asian	HB	PCR-LDR	4	60	60	45	179	183	0.902
Solerio [18]	2005	Italy	European	HB	PCR-RFLP	76	43	13	128	91	19	0.618

HWE: Hardy-Weinberg equilibrium; PB: population-based; HB: hospital-based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR: polymerase chain reaction-ligation detection reaction.

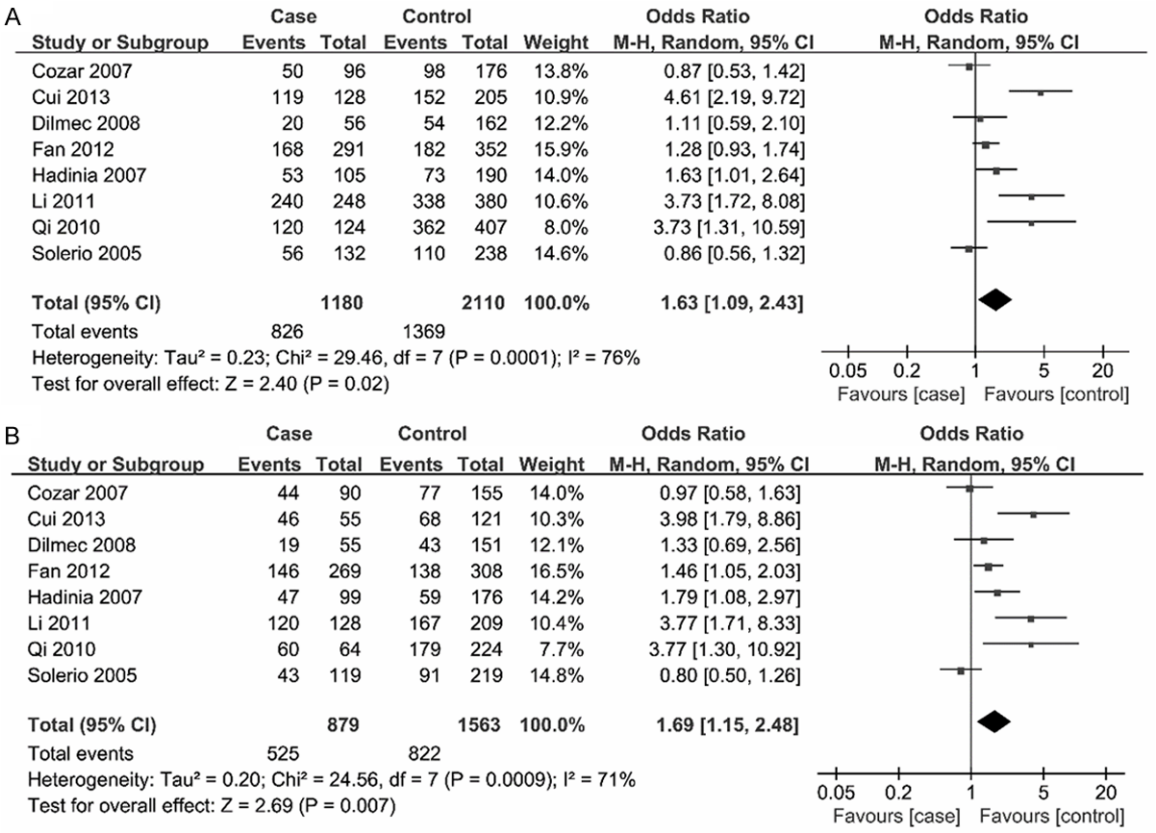

Figure 2. Forest plots for the association of CTLA-4 +49A/G polymorphism and colorectal cancer risk. A: dominant model, B: AG vs. AA.

version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

The search strategy retrieved 89 potentially relevant studies. According to the inclusion criteria, 8 studies [11-18] with full-text were included in this meta-analysis and 81 studies were excluded. The flow chart of study selection in summarized in **Figure 1**. As shown in **Table 1**, there were 8 case-control studies with 1180 CRC cases and 2110 controls concerning CTLA-4 +49A/G polymorphism. Of the 8 eligible studies, five studies [11, 13, 15, 17, 18] were writ-

Table 2. Summary of OR of the CTLA-4 +49A/G polymorphism and CRC risk

Variables	N[a]	dominant model			recessive model			AG vs. AA			GG vs. AA		
		OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2	OR (95% CI)	*P*[b]	I^2
Toatl	8	1.63 (1.09, 2.43)	0.0001	76	0.99 (0.71, 1.39)	0.02	59	1.69 (1.15, 2.48)	0.0009	71	1.41 (0.71, 2.81)	<0.0001	79
Ethnicity													
Asian	5	2.42 (1.40, 4.16)	0.002	76	1.08 (0.74, 1.56)	0.02	67	2.39 (1.52, 3.76)	0.03	61	2.12 (0.86, 5.21)	<0.0001	84
European	3	0.91 (0.68, 1.21)	0.78[c]	0	0.75 (0.43, 1.28)	0.15[c]	47	0.71 (0.45, 1.12)	0.13	52	0.72 (0.41, 1.26)	0.23[c]	32
Source of control													
PB	4	1.58(0.84, 2.98)	0.002	79	0.81(0.33, 1.98)	0.01	72	1.65(0.98, 2.80)	0.03	67	1.03(0.27, 3.91)	0.0004	83
HB	4	1.73 (0.94, 3.21)	0.002	80	1.03 (0.83, 1.27)	0.13[c]	46	1.80 (0.94, 3.46)	0.002	80	1.72 (0.72, 4.11)	0.001	81

[a]Number of comparison, [b]Test for heterogeneity, [c]Fixed-effect model was used when the *P* for heterogeneity test was >0.05, otherwise the random-effect model was used.

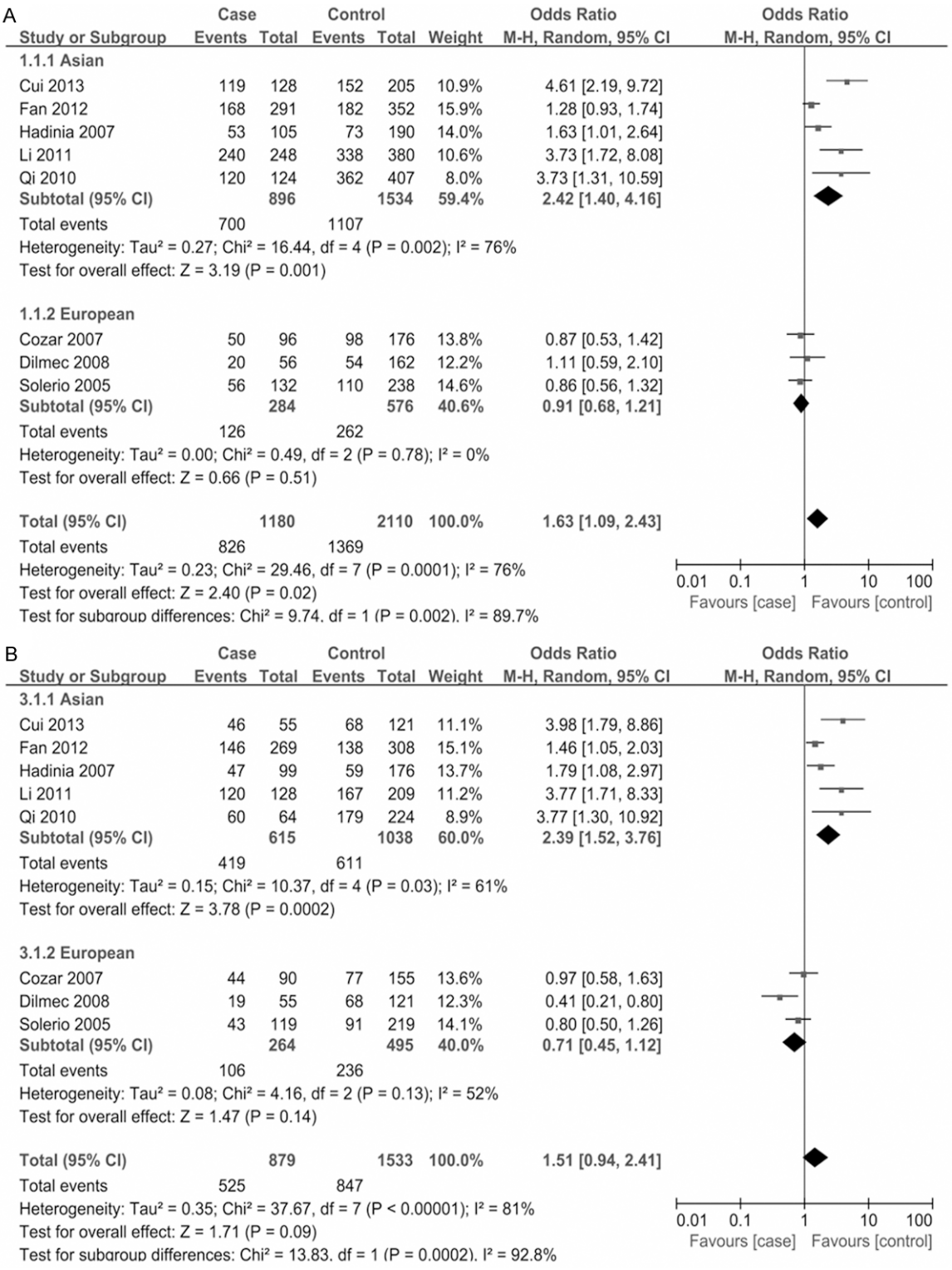

Figure 3. Forest plots for subgroup analysis by ethnicity for the association of CTLA-4 +49A/G polymorphism and colorectal cancer risk. A: dominant model, B: AG vs. AA.

ten in English and three studies [12, 14, 16] in Chinese. Two ethnicities were addressed: five studies [12, 14, 15-17] were conducted on Asian populations and three studies [11, 13,

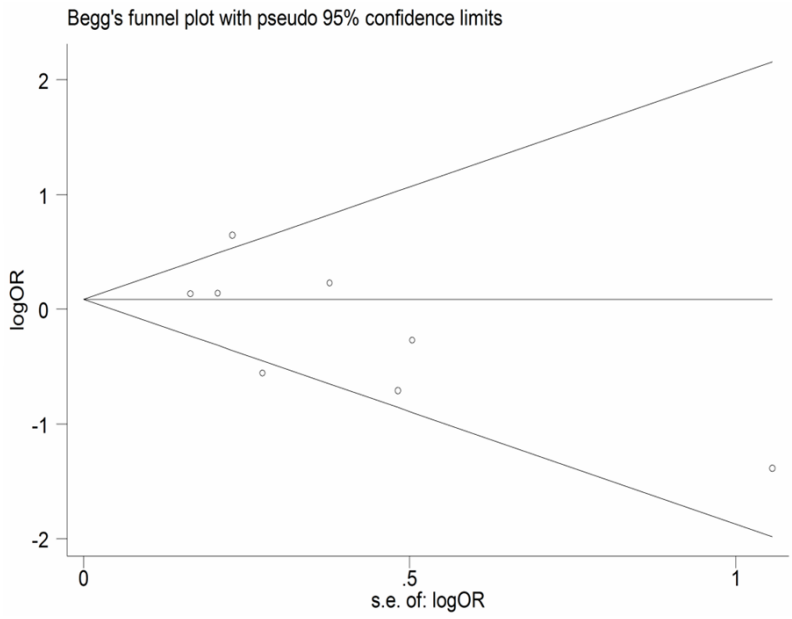

Figure 4. Begg's funnel plot for publication bias (recessive model).

18] on European populations. The distribution of genotypes in the controls was consistent with the HWE for all selected studies, except for two studies [12, 13].

Quantitative data synthesis

Overall, a significant association between the CTLA-4 +49A/G polymorphism and CRC risk was found (dominant model: OR=1.63, 95% CI: 1.09-2.43; AG vs. AA: OR=1.69, 95% CI: 1.15-2.48) (**Figure 2**). In the subgroup analysis by ethnicity, there was significant association in Asian descent (dominant model: OR=2.42, 95% CI: 1.40-4.16; AG vs. AA: OR=2.39, 95% CI: 1.52-3.76), but no significant associations between the CTLA-4 +49A/G polymorphism and the risk of CRC risk were observed in European population (dominant model: OR =0.91, 95% CI: 0.68-1.21; recessive model: OR=0.75, 95% CI: 0.43-1.28; AG vs. AA: OR=0.71, 95% CI: 0.45-1.12; GG vs. AA: OR=0.72, 95% CI: 0.41-1.26) (**Figure 3**); when stratified by source of control, no significant association was detected in both population-based and hospital-based populations (**Table 2**).

Heterogeneity and sensitivity analyses

Substantial heterogeneities were observed among studies for the association between the CTLA-4 +49A/G polymorphism and CRC risk (dominant model: I^2=76%, *P*=0.0001; AG vs. AA: I^2=71%, *P*=0.0009; GG vs. AA: I^2=79%, *P*<0.0001; recessive model: I^2=59%, *P*=0.02) (**Table 2**). Then, we assessed the source of heterogeneity for all genetic model comparison by ethnicity and source of control. The heterogeneity was partly decreased or removed in European population (dominant model: I^2=0%, *P*=0.78; AG vs. AA: I^2=52%, *P*=0.13; GG vs. AA: I^2=32%, *P*=0.23; recessive model: I^2=47%, *P*=0.15). However, there was still significant heterogeneity among Asian population, population-based and hospital-based populations. Sensitivity analysis was performed to evaluate the stability of the results. The statistical significance of the results was not altered when excluding the study that was not in HWE, confirming the stability of the results.

Publication bias

We used the Begg's funnel plot and Egger's test to address potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (**Figure 4**). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: *P*=0.080, AG vs. AA: *P*=0.115, GG vs. AA: *P*=0.955, recessive model: *P*=0.168).

Discussion

In this meta-analysis, we pooled 8 studies with 1180 cases and 2110 controls to explore the association between the CTLA-4 +49A/G polymorphism and risk of CRC. The results demonstrated that a significant association between the CTLA-4 +49A/G polymorphism and CRC risk was found in the overall comparison. Moreover, in the subgroup analysis by ethnicity, there was significant association in Asian descent; however, when stratified by source of control, we failed to detect any significant asso-

ciation in both population-based and hospital-based populations. The results in our meta-analysis were not consistent with three previous meta-analyses [24-26]. In these meta-analysis, they failed to detect a significant association between the +49A/G polymorphism and CRC risk based on five studies. The reason for which may be explained that we updated the results by adding three new studies [12, 14, 16] in our meta-analysis, which allowed for a larger number of subjects and more precise risk estimation.

CTLA-4, as a negative regulation factor of T-cell proliferation and activation, plays an important role in cancer immunosurveillance and may be involved in cancer development and progression [6]. Recently, a series of researches reported that the functional changes of CTLA-4 protein could be induced by its genetic variations (such as +49A/G polymorphism). Under this variation, it would influence the expression pattern of this protein and alter the rate of protein endocytosis [8]. Many studies have indicated that CTLA-4 +49A/G polymorphism is involved in the etiology of various cancers, such as esophageal, gastric, pancreatic, hepatocellular carcinoma and cervical cancer [27-31]. With respect to CRC, there were also several studies assessing the association. However, the results remain controversial. Qi et al [17] reported the CTLA-4 +49A/G polymorphism was associated with an increased risk of CRC in Chinese, similarly, Cui et al [12] also found that the CTLA-4 +49A/G polymorphism was related to the risk of CRC. However, Cozar et al [11] suggested that the CTLA-4 gene does not play an important role in colon cancer, in a study from Turkey, Dilmec et al [13] found that CTLA-4 gene polymorphism did not play an important role in Turkish patients with CRC. In addition, in a study from Iran, Hadinia et al [15] also reported that no statistically significant differences were found in the genotype distribution and allele frequencies among patients and controls. These inconsistent results may be attributed to differences in genetic backgrounds, environmental factors, and other factors.

In this meta-analysis, we found that individuals with AG/GG genotype had a higher risk of developing CRC under dominant and heterozygote models. The results may be explained that an A to G dimorphism at position 49 in CTLA-4 exon 1 causes an amino acid change (threonine to alanine) in the peptide leader sequence of the CTLA-4 protein and influences the ability of CTLA-4 to bind with B7.1, subsequently affects T-cell activation and then may cause the development of cancer. It has reported that the 49G allele has lower messenger RNA efficiency and decreased CTLA-4 production than the 49A allele, and individuals with the 49GG genotype may have greater T cell proliferation than those with the 49AA genotype under the condition of suboptimal stimulation. Because ethnicity can influence the results from meta-analyses, we performed subgroup analysis by ethnicity. The results showed that G allele carriers had an increasing risk of CRC compared with A allele carriers in Asian populations, but not among Europeans. Individuals from different ethnicities may have diverse genetic backgrounds and environmental factors, and consequently, the same polymorphism may play different roles in different populations [32]. In addition, only three studies on Europeans were included, which may have limited power to reveal a reliable association. Therefore, we should sensibly consider the conclusions. In the current meta-analysis, we also conducted subgroup analysis based on source of control. The +49A/G genotype distribution between CRC and control group (either population-based or hospital-based) was no significant difference.

Heterogeneity is a potential problem when interpreting the results of all meta-analysis [33]. In this meta-analysis, heterogeneity was found in overall comparison for all genetic models, when stratified by ethnicity and source of control, the heterogeneity was partly decreased or removed in European population. However, heterogeneity still existed among Asian population, population-based and hospital-based. Then sensitivity analyses were conducted by excluding the study deviating from HWE, the estimated pooled odd ratio changed quite little, strengthening the results from this meta-analysis. The results above suggest that the population selection might be the source of heterogeneity in the meta-analysis. Additionally, no publication bias was shown suggesting this possible true result.

In interpreting the current results, some limitations should be acknowledged. First, our results

were based on unadjusted estimates, without adjustment for age, gender, family history and other risk factors, while lacking of the information for the date analysis may cause serious confounding bias. Second, all recruited case-control studies were from Asians and Europeans, so our results may be applicable only to Asians and Europeans. Third, since CRC is a multi-factorial disease that results from complex interactions between many environmental and genetic factors. Therefore, when we only consider suspected gene polymorphisms in CRC neglecting the role of environmental factors, we might fail to conclude a real association.

Conclusion

In summary, this meta-analysis suggested that the CTLA-4 +49A/G polymorphism significantly increases the risk of CRC, especially for Asians. Further large and well-designed studies are warranted to validate the associations. Moreover, more sophisticated gene-gene and gene-environment interactions should be considered in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Tao Deng, Department of Gastroenterology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, Hubei Province, China. Tel: 86-27-88041911; Fax: 86-27-88042292; E-mail: dengtao1120@hotmail.com

References

[1] Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet 2014; 383: 1490-1502.

[2] Risch N. The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol Biomarkers Prev 2001; 10: 733-741.

[3] Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003; 348: 919-932.

[4] Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer 2009; 125: 171-180.

[5] Teft WA, Kirchhof MG, Madrenas J. A molecular perspective of CTLA-4 function. Annu Rev Immunol 2006; 24: 65-97.

[6] Scheipers P, Reiser H. Fas-independent death of activated CD4 (+) T lymphocytes induced by CTLA-4 cross-linking. Proc Natl Acad Sci U S A 1998; 95: 10083-10088.

[7] Sun T, Zhou Y, Yang M, Hu Z, Tan W, Han X, Shi Y, Yao J, Guo Y, Yu D, Tian T, Zhou X, Shen H, Lin D. Functional genetic variations in cytotoxic T-lymphocyte antigen 4 and susceptibility to multiple types of cancer. Cancer Res 2008; 68: 7025-7034.

[8] Ligers A, Teleshova N, Masterman T, Huang WX, Hillert J. CTLA-4 gene expression is influenced by promoter and exon 1 polymorphisms. Genes Immun 2001; 2: 145-152.

[9] Nisticò L, Buzzetti R, Pritchard LE, Van der Auwera B, Giovannini C, Bosi E, Larrad MT, Rios MS, Chow CC, Cockram CS, Jacobs K, Mijovic C, Bain SC, Barnett AH, Vandewalle CL, Schuit F, Gorus FK, Tosi R, Pozzilli P, Todd JA. The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry. Hum Mol Genet 1996; 5: 1075-1080.

[10] Harper K, Balzano C, Rouvier E, Mattei MG, Luciani MF, Golstein P. CTLA-4 and CD28 activated lymphocyte molecules are closely related in both mouse and human as to sequence, message expression, gene structure, and chromosomal location. J Immunol 1991; 147: 1037-1044.

[11] Cozar JM, Romero JM, Aptsiauri N, Vazquez F, Vilchez JR, Tallada M, Garrido F, Ruiz-Cabello F. High incidence of CTLA-4 AA (CT60) polymorphism in renal cell cancer. Hum Immunol 2007; 68: 698-704.

[12] Cui JY, Ma H, Cui WL, Ma WH, Qi YQ. Association of cytotoxic T lymphocyte antigen-4 gene polymorphism with susceptibility on colorectal cancer. Chin J Curr Adv Gen Surg 2013; 16: 127-130.

[13] Dilmec F, Ozgonul A, Uzunkoy A, Akkafa F. Investigation of CTLA-4 and CD28 gene polymorphisms in a group of Turkish patients with colorectal cancer. Int J Immunogenet 2008; 35: 317-321.

[14] Fan ZG, Fu J, Chen T, Wang GJ. A study of relationship between cytotoxic T lymphocyte antigen-4 +49A>G gene polymorphism and colorectal cancer. Heilongjiang Medical Jounal 2012; 36: 810-811.

[15] Hadinia A, Hossieni SV, Erfani N, Saberi-Firozi M, Fattahi MJ, Ghaderi A. CTLA-4 gene promoter and exon 1 polymorphisms in Iranian patients with gastric and colorectal cancers. J Gastroenterol Hepatol 2007; 22: 2283-2287.

[16] Li XD, Zhao JP, Sun YY. Relationship between cytotoxic T lymphocyte associated antigen-4 +49A>G gene polymorphism and colorectal cancer in Chinese. Chin J Biologicals 2011; 24: 1038-1041.
[17] Qi P, Ruan CP, Wang H, Zhou FG, Xu XY, Gu X, Zhao YP, Dou TH, Gao CF. CTLA-4 +49A>G polymorphism is associated with the risk but not with the progression of colorectal cancer in Chinese. Int J Colorectal Dis 2010; 25: 39-45.
[18] Solerio E, Tappero G, Iannace L, Matullo G, Ayoubi M, Parziale A, Cicilano M, Sansoè G, Framarin L, Vineis P, Rosina F. CTLA4 gene polymorphism in Italian patients with colorectal adenoma and cancer. Dig Liver Dis 2005; 37: 170-175.
[19] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.
[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[21] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.
[22] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.
[23] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[24] Geng R, Song F, Yang X, Sun P, Hu J, Zhu C, Zhu B, Fan W. Association between cytotoxic T lymphocyte antigen-4 +49A/G, -1722T/C, and -1661A/G polymorphisms and cancer risk: a meta-analysis. Tumour Biol 2013; 35: 3627-3639.
[25] Zhang Y, Zhang J, Deng Y, Tian C, Li X, Huang J, Fan H. Polymorphisms in the cytotoxic T-lymphocyte antigen 4 gene and cancer risk: a meta-analysis. Cancer 2011; 117: 4312-4324.
[26] Zheng J, Yu X, Jiang L, Xiao M, Bai B, Lu J, Zhou Y. Association between the Cytotoxic T-lymphocyte antigen 4 +49G>A polymorphism and cancer risk: a meta-analysis. BMC Cancer 2010; 10: 522.
[27] Cheng XL, Ning T, Xu CQ, Li Y, Zhu BS, Hou FT, Zhang SY, Chen ZP. Haplotype analysis of CTLA4 gene and risk of esophageal squamous cell carcinoma in Anyang area of China. Hepatogastroenterology 2011; 58: 432-437.
[28] Hou R, Cao B, Chen Z, Li Y, Ning T, Li C, Xu C, Chen Z. Association of cytotoxic T lymphocyte-associated antigen-4 gene haplotype with the susceptibility to gastric cancer. Mol Biol Rep 2010; 37: 515-520.
[29] Yang M, Sun T, Zhou Y, Wang L, Liu L, Zhang X, Tang X, Zhou M, Kuang P, Tan W, Li H, Yuan Q, Yu D. The functional cytotoxic T lymphocyte-associated protein 4 49G-to-a genetic variant and risk of pancreatic cancer. Cancer 2012; 118: 4681-4686.
[30] Hu L, Liu J, Chen X, Zhang Y, Liu L, Zhu J, Chen J, Shen H, Qiang F, Hu Z. CTLA-4 gene polymorphism +49 A/G contributes to genetic susceptibility to two infection-related cancers-hepatocellular carcinoma and cervical cancer. Hum Immunol 2010; 71: 888-891.
[31] Sun T, Hu Z, Shen H, Lin D. Genetic polymorphisms in cytotoxic T-lymphocyte antigen 4 and cancer: the dialectical nature of subtle human immune dysregulation. Cancer Res 2009; 69: 6011-6014.
[32] Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K. A comprehensive review of genetic association studies. Genet Med 2002; 4: 45-61.
[33] Boccia S, De Feo E, Gallì P, Gianfagna F, Amore R, Ricciardi G. A systematic review evaluating the methodological aspects of meta-analyses of genetic association studies in cancer research. Eur J Epidemiol 2010; 25: 765-775.