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Current Evidence on the Association between Cytotoxic T-Lymphocyte Antigen 4 +49G > A Polymorphism and Digestive System Cancer Risks: a Meta-analysis Involving 11,923 Subjects

Biao Jiang, Meng Ji, Ailiang Wang, Wei Zhang, Zhixin Zhang and Qiang Li*

Tianjin Cancer Institute and Hospital, Tianjin, China

Abstract

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) plays an important role in downregulating T cell activation and proliferation. The CTLA-4 +49G > A polymorphism is one of the most commonly studied polymorphisms in this gene due to its association with many cancer types, but the association between CTLA-4 +49G > A polymorphism and digestive system cancer risks remain inconclusive. An updated meta-analysis based on 17 independent case-control studies consisting of 5,176 cancer patients and 6,747 controls was performed to address this association. Overall, there was no statistically increased risk of digestive system cancers in every genetic comparison.In subgroup analysis, this polymorphism was significantly linked to higherrisks for pancreatic cancer (GG vs. AA, OR=1.976, 95% CI = 1.496-2.611; GA *vs.* AA, OR=1.433, 95% CI = 1.093-1.879; GG/GA *vs.* AA, OR=1.668, 95% CI = 1.286-2.164; GG *vs.* GA/AA, OR = 1.502, 95% CI = 1.098-2.054; G *vs.* A, OR=1.394, 95%CI = 1.098-1.770). We also observed increased susceptibility of hepatocellular cell carcinoma in homozygote comparison (OR=1.433, 95% CI = 1.100-1.866) and dominant model (OR=1.360, 95% CI = 1.059-1.746). According to the source of controls, significant effects were only observed in hospital-based studies (GA/AA *vs.* GG, OR=1.257, 95% CI = 1.129-1.399). In the stratified analysis by ethnicity, No significantly increased risks were found in either Asian or Caucasian. Our findings suggest that the CTLA-4 +49G > A polymorphism may be not associated with an elevated digestive system cancer risks.

Keywords: CTLA-4; Polymorphisms; Cancer; Meta-analysis

Introduction

CTLA-4, a member of the immunoglobulin super-family, is a co-stimulatory molecule expressed by activated T cells and has the function of down-regulating T-cell activation [1]. CTLA-4 can also induce FAS-independent apoptosis of activated T cells, which may further inhibit immune function of T lymphocytes. A list of mechanisms of CTLA-4 function have been indicated, such as ligand competition with the positive T-cell co-stimulatory CD28 molecule, interference of TCR signaling, and inhibition of cyclin D3 and cyclin-dependent kinases production [2]. In tumor-transplanted mice, injection with antibodies that block CTLA-4 function enhanced T cell activation [3], rejected a variety of different tumors, and had long-lasting anti-tumor immunity [4], suggesting that the CTLA-4 may play an important role in carcinogenesis.

The CTLA-4 gene is located on chromosome 2q33, consisting 4 exons that encode separate functional domains: a leader sequence, an extracellular domain, a transmembrane domain, and a cytoplasmic domain [5-7]. This gene is polymorphic and more than 100 single nucleotide polymorphisms have been identified [8]. An common polymorphism at position 49 in CTLA-4 exon 1 (rs231775), which causes an amino acid change (threonine to alanine) in the peptide leader sequence of the CTLA-4 protein [9]. Recent studies indicated that this polymorphism may influence the ability of CTLA-4 to bind with B7.1 and affect T-cell activation subsequently [10,11].

Previous studies have identified that this polymorphism is associated with different cancers including lung cancer, breast cancer, and cervical cancer [10,12]. However, the results of studies on the association between the +49 A > G polymorphism and the risk of digestive system cancers remain inconsistent [10,13-26]. To improve the efficiency of meta-analysis on digestive cancers and reduce the potential between-study heterogeneity which might derive from various cancers in diverse systems, we focused on digestive system cancers only and added more recent studies in this meta-analysis.

Search Strategy

In this meta-analysis, a comprehensive literature research of the US National Library of Medicine's Pub Med database, ISI Web of Knowledge, Medline, Embase and Google Scholar Search (update to November, 2012) were conducted using the search terms including "CTLA-4", "polymorphisms", "cancer", and the combined phrases in order to obtain all genetic studies on the relationship of CTLA-4 + 49G/A polymorphism and cancer. We also used a hand search of references of original studies or reviewed articles on this topic to identify additional studies. The following criteria was used to select the eligible studies: (1) a case–control study on the association between CTLA-4 + 49G/A polymorphism and cancer; (2) detailed number of different genotypes for estimating an odds ratio (OR) with 95% confidence interval; (3) when several publications reported on the same population data, the largest or most complete study was chosen.

Data Extraction

Data extraction was carried out independently by two investigators after the concealment of authors, journals, supporting organizations

***Corresponding author:** Qiang Li, Tianjin Cancer Institute and Hospital, Tianjin, China, E-mail: liqiang4012@yahoo.cn

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and funds to avoid investigators' bias. For each eligible study, the following information was recorded: the first author's name, the year of publication, country of origin, cancer type, genotyping method, sources of controls, racial descent of the study population, number of cases and number of controls with different allele frequencies.

Statistical Analysis

The strength of relationship between CTLA-4 + 49G/A polymorphism and cancer was assessed by using Crude OR with 95% CI. We examined the association between the CTLA-4 + 49G/A polymorphism and digestive cancer risks using the following genetic contrasts: homozygote comparison (GG *vs.* AA), heterozygote comparison (GA *vs.* AA), dominant genetic model (GG + GA *vs.* AA), recessive genetic model (GG *vs.* GA + AA) and allelic comparison (G *vs.* A). Between-study heterogeneity was evaluated by Q-test. Fixed effects model was used to pool the data when the P-value of Q-test ≥ 0.05, otherwise, random-effects model was selected. Both funnel plot and Egger's test were used to assess the publication bias. (P<0.05 was considered representative of statistical significance). All statistical analyses were performed using STATA11.0 software and Review Manage (v.5; Oxford, England).

Results

Eligible studies

By the inclusion and exclusion criteria, 17 relevant studies involving 5,176 cases and 6,747 controls were selected in this meta-analysis. The main characteristics of these studies are shown in table 1. Genotype distribution of the CTLA-4 + 49G/A polymorphism among cancer cases and controls of the 17 studies are shown in table 2. All studies were case–control studies, including five colorectal cancer studies, four gastric cancer studies, two esophageal cancer studies, two hepatocellular cell carcinoma studies, two oral cancer studies and two pancreatic cancer studies. There were 12 studies of Asian descent and five studies of Caucasian descent. Hospital based controls were carried out in 12 studies, while population based controls were carried out in 5 studies. The genotyping method contains the classic polymerase chain reaction–restriction fragment length polymorphism assay(PCR-RFLP), RFLP and Taqman. The distribution of genotypes in the controls was all in agreement with HWE.

Meta-analysis

The association strength between CTLA-4 + 49G/A polymorphism and the susceptibility for digestive system cancers are shown in table 3. Overall, there was no statistically increased risk of digestive system cancers in every genetic comparison (GG *vs.* AA, OR=1.217, 95% CI = 0.923–1.605; GA *vs.* AA, OR=1.161, 95% CI = 0.991–1.360; GG/GA *vs.* AA, OR=1.165, 95% CI = 0.932–1.456; GG *vs.* GA/AA, OR=1.114, 95% CI = 0.948–1.312; G *vs.* A, OR= 0.966, 95% CI = 0.829–1.126).

We then evaluated the effects of CTLA-4 + 49G/A polymorphism according to specific cancer types, different ethnicities and different sources of control. As shown in table 3, we demonstrated that this locus polymorphism was significantly linked to higherrisks for pancreatic cancer (GG *vs.* AA, OR=1.976, 95% CI = 1.496-2.611; GA *vs.* AA, OR=1.433, 95% CI = 1.093-1.879; GG/GA *vs.* AA, OR=1.668, 95% CI =1.286-2.164; GG *vs.* GA/AA, OR=1.502, 95% CI = 1.098-2.054; G *vs.* A, OR=1.394, 95%CI = 1.098-1.770). We alsoobserved increased susceptibility of hepatocellular cell carcinoma in homozygote comparison (OR=1.433, 95% CI = 1.100-1.866) and dominant model (OR = 1.360, 95% CI = 1.059-1.746). Furthermore, we observed increased susceptibility of esophageal cancer only in heterozygote comparison (OR=1.454, 95% CI = 1.110-1.906). No significant associations were found in colorectal cancer, gastric cancer and oral cancer.

According to the source of controls, significanteffects were observed in hospital-based studies (GA/AA *vs.* GG, OR=1.257, 95% CI = 1.129-

Author	Year	Type	Ethnicity	Country	Genotye Assay	Source of Control	Cases	Controls
Yang	2012	Pancreatic	Asian	China	PCR-RFLP	Population	926	368
Lang	2012	Pancreatic	Asian	China	PCR-RFLP	Population	651	602
Cheng	2011	Esophagus	Asian	China	PCR-RFLP	Population	205	205
Cozar	2007	Colon,	European	Spain	TaqMan	Hospital	176	221
Dilmec	2008	Colorectal	European	Turkey	RFLP	Hospital	162	56
Gu	2010	Hepatocellular	Asian	China	PCR-LDR	Hospital	367	407
Hadinia	2007	Colorectal	Asian	Iran	RFLP, PCR-ARMS	Hospital	190	105
Hadinia	2007	Gastric	Asian	Iran	RFLP, PCR-ARMS	Hospital	190	43
Hu	2010	Hepatocellular	Asian	China	TaqMan	Population	854	853
Hou	2010	Gastric	Asian	China	PCR-ARMS	NA	205	262
Kammerer	2010	Oral	European	German	RT-PCR	Hospital	40	83
Mahajan	2008	Gastric	European	Poland	TaqMan	Population	411	301
Qi	2010	Colorectal	Asian	China	PCR-LDR	NA	124	407
Solerio	2005	Colorectal	European	Italy	RFLP	Hospital	238	132
Sun	2008	Esophagus	Asian	China	RFLP	Hospital	1008	1010
Sun	2008	Gastric	Asian	China	RFLP	Hospital	530	530
Wong	2006	Oral	Asian	China	RFLP	Hospital	147	118

Table 1: Main characteristics of included studies in the meta-analysis.

Author	Year	Type	AA (control)	AG (control)	GG (control)	AA (case)	AG (case)	GG (case)	G (control)	A (control)	G (case)	A (case)	HWE
Gu	2010	Hepatocellular	51	166	150	45	179	183	268	466	269	545	YES
Hu	2010	Hepatocellular	106	380	367	79	376	399	592	1114	534	1174	YES
Hadinia	2007	Gastric	24	13	6	117	59	14	25	61	87	293	YES
Mahajan	2008	Gastric	89	153	59	152	189	70	331	271	493	329	YES
Hou	2010	Gastric	100	55	107	41	70	94	269	255	258	152	YES
Sun	2008	Gastric	60	235	235	39	209	282	355	705	287	773	YES
Qi	2010	Colorectal	4	60	60	45	179	183	68	180	269	545	YES
Solerio	2005	Colorectal	76	43	13	128	91	19	195	69	347	129	YES
Hadinia	2007	Colonrectal	52	47	6	117	59	14	59	151	87	293	YES
Cozar	2007	Colorectal	119	87	15	78	77	21	325	117	233	119	YES
Dilmec	2008	Colorectal	36	19	1	108	43	11	21	91	65	259	YES
Cheng	2011	Esphogaous	36	79	90	46	105	54	259	151	213	197	YES
Sun	2008	Esphogaous	128	434	448	73	406	529	690	1330	552	1464	YES
Kammerer	2010	Oral	35	32	16	11	23	6	102	64	45	35	YES
Wong	2006	Oral	12	58	48	25	64	58	82	154	114	180	YES
Yang	2012	Pancreatric	50	178	140	70	374	482	458	278	1338	514	YES
Lang	2012	Pancreatic	82	312	208	62	326	263	728	476	852	450	YES

Table 2: Distribution of CTLA-4 + 49G/A polymorphism among cancer cases and controls in this meta-analysis.

Study groups	*N* *	GG vs. AA		GA vs. AA		GG/GA vs. AA		GG vs. GA/AA		G vs. A	
		OR (95% CI)	*P*$	OR (95% CI)	*P*$	OR (95% CI)	*P*$	OR (95% CI)	*P*$	OR (95% CI)	*P*$
Total	17	1.217 (0.923-1.605) ‡	<0.001	1.161 (0.991-1.360)‡	<0.001	1.165 (0.932-1.456)‡	<0.001	1.114 (0.948-1.312)‡	<0.001	0.966 (0.829-1.126)‡	<0.001
Cancer type											
Hepatocellular	2	1.433 (1.100-1.866)	0.851	1.291 (0.992-1.681)	0.771	1.360 (1.059-1.746)	0.796	1.168 (0.996-1.367)	0.920	0.857 (0.761-0.964)	0.983
Gastric	4	1.160 (0.601-2.237)‡	<0.001	1.300 (0.670-2.521)‡	<0.001	1.235 (0.662-2.302)‡	<0.001	1.077 (0.814 -1.508) ‡	0.042	1.033 (0.696-1.532)‡	<0.001
Colorectal	5	1.028 (0.479-2.207)‡	0.020	0.805 (0.498-1.301)‡	0.006	0.858 (0.543-1.354)‡	0.006	1.079 (0.804-1.447)	0.215	0.929 (0.727-1.188)‡	0.060
Esophagus	2	1.004 (0.235-4.295)‡	<0.001	1.454 (1.110-1.906)	0.146	1.194 (0.482-2.957)‡	0.002	0.809 (0.273-2.398)‡	<0.001	0.708 (0.627-0.799)	0.368
Oral	2	0.725 (0.379-1.385)	0.312	1.086 (0.259-4.554)‡	0.013	1.017 (0.300-3.449)‡	0.026	0.876 (0.563-1.364)	0.478	1.058 (0.786-1.424)	0.240
Pancreatic	2	1.976 (1.496-2.611)	0.173	1.433 (1.093-1.879)	0.766	1.668 (1.286-2.164)	0.347	1.502 (1.098-2.054)‡	0.033	1.394 (1.098-1.770)‡	0.049
Ethnicity											
Asian	12	1.240 (0.908-1.695)‡	<0.001	1.164 (0.895-1.514)‡	<0.001	1.179(0.896-1.551)‡	<0.001	1.139 (0.956 -1.356)‡	<0.001	0.974 (0.807-1.175)‡	<0.001
European	5	1.143 (0.660-1.977)‡	0.043	0.988 (0.699-1.397)‡	0.021	1.101(0.776-1.562)‡	0.029	1.015 (0.763 -1.351)	0.154	0.951 (0.745-1.213)	0.053
Source of Control Population-based	5	1.169 (0.694-1.970)‡	<0.001	1.156 (0.873-1.530)‡	0.029	1.170(0.800-1.712)‡	<0.001	0.965 (0.678-1.373)‡	<0.001	1.063 (0.802-1.408)‡	<0.001
Hospital-based	12	1.255 (0.901-1.749)‡	0.001	1.125 (0.828-1.530)‡	<0.001	1.154(0.864-1.541)‡	<0.001	1.257 (1.129-1.399	0.150	0.919 (0.778-1.086)‡	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

* Studies of comparison,$P-value of Q-test for heterogeneity test, ‡ Random model was used.

Table 3: Results of meta-analysis for CTLA-4 + 49G/A polymorphism and digestive cancer risks.

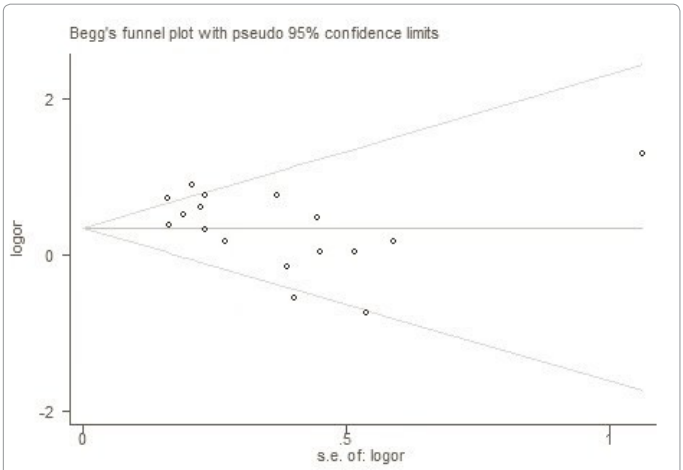

Figure 1: The funnel plot of overall GG *vs.* AA.

1.399), but in population-based studies, no significant association was observed in all models. In the stratified analysis by ethnicity, no significantly increased risks were found in either Asian or Caucasian.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis (Figure 1 shows the funnel plot of overall GG *vs.* AA). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not present any obvious evidence of publication bias in the subgroup analyses.

Discussion

The result of this meta-analysis suggested that CTLA-4 + 49G/A polymorphism was not overall significantly associated with digestive system cancer risk. In stratified analysis by ethnicity, we also failed to detect any significant association in either Asian or Caucasian. However, in subgroup analysis, this polymorphism was significantly linked to higher risks for pancreatic cancer. Besides, when stratified according to study design, positive associations were observed in hospital-based studies.

The CTLA-4 49G>A SNP has been linked to elevated risk of breast cancer in an Iranian population [6], and non–Hodgkin's lymphoma in an European Caucasian population [26]. In addition, two more studies suggested that this polymorphism is associated with different cancers including lung cancer and cervical cancer [10,21]. A meta-analysis conducted by Zheng et al. suggested that the CTLA-4 + 49G/A polymorphism was associated with an increased risk of developing solid tumors (including lung cancer, breast cancer, colorectal cancer, gastric cancer, skin cancer, thymoma, nasopharyngeal carcinoma, cervical squamous cell carcinoma, esophageal cancer, oral squamous cell carcinoma, HBV-related hepatocellular carcinoma, and renal cell cancer [27]. Interestingly, Zhang et al. conducted a meta-analysis and the results indicated that the polymorphism is associated with a decreased risk of lung cancer and breast cancer but not of cervical cancer, colorectal cancer, or gastric cancer [28].

In our analysis, we first reported that there was no statistically increased risk between the CTLA-4 + 49G/A polymorphism and digestive system cancers. In subgroup analysis, we observed this polymorphism was significantly linked to higher risks for pancreatic cancer. We also observed the CTLA-4 + 49G/A polymorphism was associated with an increased risk of developing hepatocellular cell carcinoma but not gastric cancer, colorectal cancer and oral cancer. However, all of these results should be interpreted with caution. On condition that, for some cancer types, only two case-control studies were included, which may have limited power to reveal a reliable association. Furthermore, we observed inconsistent results between hospital-based studies and population-based studies, which may be explained by the biases brought by hospital-based studies, controls in hospital-based studies may be less representative of general population than controls from population-based studies.

There were some limitations in our meta-analysis. Firstly, sample size in any given cancer was not sufficiently large. It might be difficult to get a concrete conclusion if the number of included studies in subgroup was few. Secondly, due to the original data of the eligible studies were unavailable, it is difficult for us to evaluate the roles of some special environmental factors and lifestyles such as diet, alcohol consumption, and smoking status in developing cancer. And thirdly, language bias might derive from the screened references of English documents only.

In conclusion, our meta-analysis suggested that the CTLA-4 + 49G/A polymorphism may be not associated with an elevated digestive system cancer risks. Large well-designed epidemiological studies are needed to validate our findings.

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