RESEARCH ARTICLE

Adiponectin Receptor 1 (ADIPOR1) rs1342387 Polymorphism and Risk of Cancer: a Meta-analysis

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Abstract

Many studies have indicated possible associations between a polymorphism of adiponectin receptor 1 (ADIPOR1) rs1342387 and risk of cancer, but contradictory results have been reported. The main aim of this study was to draw a reliable conclusion about the relationship between the rs1342387 polymorphism and cancer incidence, by conducting a literature search of Pubmed, Embase, Wanfang and Cochrane libraries. Eleven studies including 3, 738 cases and 4, 748 controls were identified in this meta-analysis. The ADIPOR1 rs1342387 polymorphism was associated with risk of colorectal cancer for all genetic comparison models (GG *vs* AA, OR: 1.44, 95%CI: 1.21 -1.70; G carriers *vs* A carriers, OR: 1.23, 95%CI: 1.11 -1.36; dominant model, OR: 1.28, 95%CI: 1.10 -1.49 and recessive model, OR: 1.31, 95%CI: 1.12 -1.55). Stratified by ethnicity, the rs1342387 polymorphism was significantly associated with risk of colorectal cancer in Asian ancestry for all genetic comparison models (GG *vs* AA, OR: 1.56, 95%CI: 1.26-1.92; G carriers vs. A carriers OR: 1.30, 95%CI: 1.18 -1.43; dominant model OR: 1.31, 95%CI: 1.08 -1.60 and recessive model OR: 1.44, 95%CI: 1.26 -1.64), but not in Caucasian or mixed (Caucasian mainly) groups. In summary, the ADIPOR1 rs1342387 polymorphism is significantly associated with risk of colorectal cancer among individuals of Asian ancestry.

Keywords: Adiponectin receptor 1 - polymorphism - rs1342387 - cancer - meta-analysis - Asian ancestry

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Introduction

Cancer and obesity are two major public health problems of this century. In 2008, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred all over the world (Ferlay et al., 2010), and in the same year, about 1.46 billion adults were overweight worldwide, of whom estimated 500 million adults were obese (Finucane et al., 2011). Epidemiological studies had established that increasing of BMI and excess body weight were risk factors for some cancers, such as colorectal cancer, prostate cancer and renal cancer, which were called obesity-related cancers (Renehan et al., 2008; Vucenik and Stains, 2012). Recent studies had revealed that adiponectin, the most abundant adipose-tissue protein, was a key player in the development and progression of obesity-related cancers (Barb et al., 2007; Paz-Filho et al., 2011; Liu et al., 2013). Adiponectin is involved in anti-inflammatory, insulin-sensitizing, and anti-proliferation activities which are associated with the development of cancer (Barb et al., 2007; Ziemke and Mantzoros, 2010). Recent studies have confirmed that adiponectin implement the main biological function by signaling through its receptors- ADIPOR 1 and ADIPOR 2 (Kim et al., 2010), which are expressed in various of malignancies including colorectal cancer, breast cancer, prostate cancer and so on (Kim et al., 2010; Dalamaga et al., 2012). The higher expression of AdipoR1, the stronger growth inhibitory effect of adiponectin was observed in cancer cell lines (Tsukada et al., 2011). A down-regulation of AdipoR1 by specific siRNA could also significantly suppress the antiproliferative effects of adiponectin (Ishikawa et al., 2007). Although the functional of adiponectin receptors in cancer cells has not been fully explained, the AMP-activated protein kinase (AMPK) may play an important role in the limits of cancer cell lines proliferation by adiponectin and its receptors (Kim et al., 2010). In addition, genetic factors, such as genetic polymorphism, could play an extremely important role in cancer susceptibility.

rs1342387 is a A/G variation in the ADIPOR1 gene on human chromosome 1, and it has been reported to be significantly associated with obesity (Siitonen et al., 2006) and insulin resistance (Crimmins and Martin, 2007). Kaklamani et al. (2008) firstly reported the association of polymorphisms of ADIPOR1 with colorectal cancer risk, and in Study 1 of his research, rs1342387 CC/TC genotypes were correlation with an increased risk

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of colorectal cancer, but in the validation study, this association was not confirmed. He et al. (He et al., 2011) reported that, in Chinese population, carriers with allele A of rs1342387A/G had a much lower risk of colorectal cancer than nocarriers (G/G). Nevertheless, related studies on rs1342387 polymorphism in cancer had shown contradictory results. Beebe Dimmer et al. (2010) did not discover the link between rs1342387 polymorphism and risk of prostate cancer in African American men. Li Liu et al. (2011) did not observer the association between rs1342387 polymorphism and risk of colorectal cancer in Chinese.

Because of the important functions of ADIPOR1 in link of obesity and cancer, and the contradictory of current studies, we performed this meta-analysis to draw a reliable conclusion about the relationship between ADIPOR1 rs1342387 polymorphism and cancer incidence by enlarging the sample size and stratified analysis.

Materials and Methods

Search strategy and selection criteria

We systematically searched the databases of Pubmed, Embase, Wanfang and Cochrane library, with the latest update by 30 August 2013, by using the following search terms: "Adiponectin Receptor" or "ADIPOQ Receptor" or "ADIPOR1" or "ADIPOR2", "Cancer" or "Tumor" or "Carcinoma" and "Polymorphism" or "Variant" or "Genotype". There was no language limitation for literature searching. Literature search and selection was conducted by two investigators (Lixiang Yu and Liyuan Liu) independently, and contradictions were solved by discussion with the third author (Fei Wang).

The studies must meet the following criteria: (a) the study must be a case-control study, (b) the study must explore the relationships between ADIPOR1 rs1342387 polymorphism and risk of cancer, (c) the study must provide the necessary data for analysis, including the number of each genotype incase and control groups, (d) if multiple articles were reported on the same or overlapping data, the article with largest size or latest publication was selected. Case report, review or editorial were excluded from our analysis.

Data extraction

The following information of each study was extracted: first author's name, year of publication, country and ethnicity of participants, type of cancer, source of control group (hospital-based or population-based), genotype method, number of case and control group, number of each genotype in case and control group. Hospital-based study was defined as controls were from patients without cancer, and population-based study from healthy population. The Newcastle-Ottawa Scale (NOS) was used to evaluate the qualities of eligible studies (Wells et al., 2000).

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) of rs1342387 genotype was tested by chi-square test for the control group. Odds ratio (OR) and corresponding 95% confidence interval (95%CI) were used to evaluate the strength of the associations between rs1342387 polymorphism and risk of cancer. The pooled ORs of the following genetic comparison models were calculated: GG *vs* AA, G carriers *vs* A carriers, dominant model (GG+GA *vs* AA) and recessive model (GG *vs* GA+AA). I-squared test was used to evaluate the heterogeneity among studies. If $I^2 \geq 50\%$ or $p_h < 0.10$ of Cochrane Q test, the heterogeneity was regarded as statistical significant (Higgins et al., 2003), and the pooled ORs were calculated by the random-effect (DerSimonian and Laird method) model (DerSimonian and Laird, 1986). Otherwise, the fixed-effect (Mantel-Haenszel method) model was used (MANTEL and HAENSZEL, 1959). Subgroup analyses were conducted according to cancer types, ethnicity and source of controls. Sensitivity analysis was conducted to assess the influence of studies on the reliability of combined analysis by sequential removal of individual studies. Publication bias was assessed by Begg and Egger regression tests (Begg and Mazumdar, 1994; Egger et al., 1997). All statistical tests were done using STATA software (version 11.0; Stata Corporation, College Station, TX). A p value<0.05 indicated statistical significance.

Results

Characteristics of studies

The process of literature selection was shown in Figure 1. A total of 8 literatures (11 studies) including 3, 738 cases and 4748 controls were identified in this meta-analysis (Kaklamani et al., 2008a; 2008b; Beebe-Dimmer et al., 2010; He et al., 2011; Kaklamani et al., 2011; Liu et al., 2011; Ou, 2012; Zhang et al., 2012), and one of these literatures was doctoral dissertation (Ou, 2012). All of the 11 studies were case-control studies, nine of which were population-based and another two were hospital-based. The cancer types included colorectal cancer (CRC) (6 studies), prostate cancer (PC) (2 studies), breast cancer (BC) (1 study), gastric cancer (GC) (1 study) and liver cancer (LC) (1 study). There were 6 studies for Asians, 1 study for African Americans and 4 studies for Caucasians or mixed (Caucasian mainly). The genotypes of control groups of all studies were fitting for Hardy-Weinberg

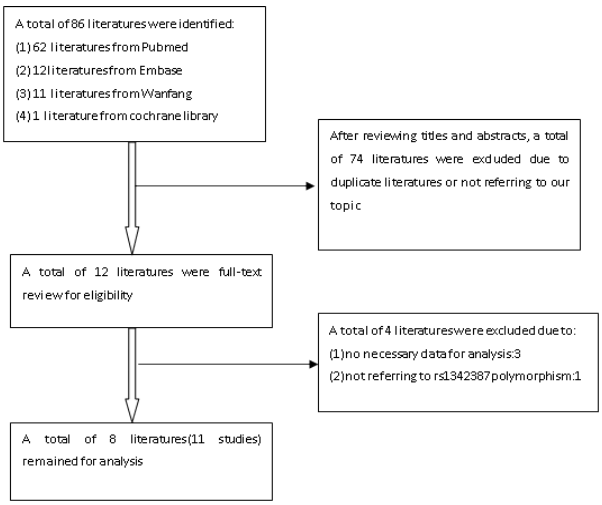

Figure 1. Flow Chart Showed the Process for Selection of Literatures in this Meta-analysis

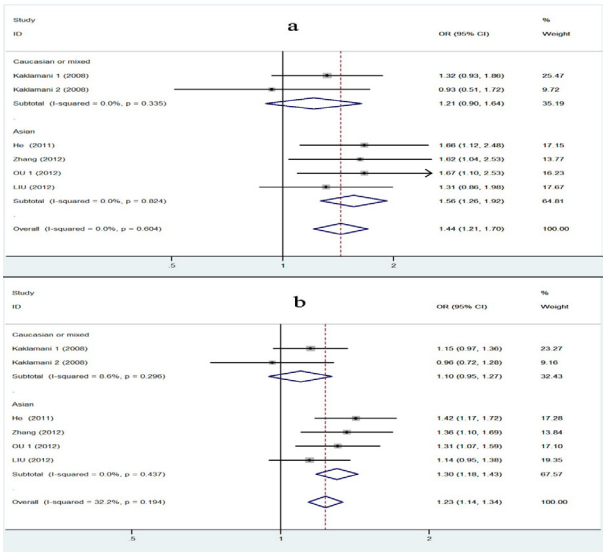

Figure 2. Forest Plots of Subgroup Analyses by Ethnicity for GG *vs* AA model (a) and G Carriers *vs* A Carriers Model (b) with the Risk of CRC. A) In GG *vs* AA model, GG genotype of ADIPOR1 rs1342387 polymorphism significantly associated with increased risk of CRC compared with AA genotype for Asian. Fixed-effect model was used. **B)** In G carriers *vs* A carriers model, G carriers of ADIPOR1 rs1342387 polymorphism significantly associated with increased risk of CRC compared with A carriers for Asian. Fixed-effect model was used

equilibrium (HWE) (p>0.05). Two of the studies were categorized as low quality with 6 stars by the Newcastle-Ottawa Scale (NOS). The characteristics of selected studies are shown in Table 1.

ADIPOR1 rs1342387 polymorphism and risk of cancer

Significant associations of ADIPOR1 rs1342387 polymorphism with risk of cancer were found in GG *vs* AA (OR: 1.22, 95%CI: 1.07-1.38, p_z=0.003), G carriers *vs* A carriers (OR: 1.13, 95%CI: 1.03-1.25, P_z =0.010) and Recessive model (OR: 1.20, 95%CI:1.05-1.37, P_z =0.006). There was no association between Dominant model and risk of cancer (OR: 1.11, 95%CI: 1.00-1.24, P_z =0.056). (Table 2)

Significant heterogeneity were observed in G carriers *vs* A carriers and Recessive model (I^2%=52.7, P_h=0.020 and I^2%=46.5, P_h=0.044). When subgroup analyses were carried out by cancer types, the heterogeneity were effectively reduced in G carriers *vs* A carriers (cancer type: I^2%=32.2, P_h=0.194 for CRC, I^2%=0.0, P_h=0.947 for PC, I^2%=0.0, P_h=0.814 for other cancers). Significant relationships between rs1342387 polymorphism and colorectal cancer risk were found for all genetic comparison models (Table 2).

Stratified by ethnicity, rs1342387 polymorphism was

Table 1. The Basic Information of Studies Included in this Meta-analysis

Study	Year	Country	Ethnicity	Cancer type	Source of control	Genotype method	Case (n)	Control (n)	Genotype (Case / Control, n) GG	AG	AA	NOS scores	HWE χ^2	P
Kaklamani 1	2008	USA.	Caucasian	CRC	PB	Taqman	435	647	113/155	223/313	99/179	8	0.63	0.43
Kaklamani 2	2008	USA.	Mixed	CRC	HB	Taqman	190	192	57/61	101/99	32/32	9	0.59	0.44
Kaklamani 3	2008	USA.	Mixed	BC	PB	Taqman	708	808	145/180	362/419	201/209	7	1.2	0.27
Beebe Dimmer	2010	USA.	African	PC	PB	Taqman	131	333	41/87	59/172	31/74	6	0.4	0.53
He	2011	China	Asian	CRC	PB	PCR-RFLP	420	555	213/210	157/263	50/82	7	0	0.98
Kaklamani 4	2011	USA.	Mixed	PC	PB	Taqman	446	438	116/107	218/209	112/122	8	0.87	0.35
Zhang	2012	China	Asian	CRC	PB	PCR-RFLP	370	370	180/140	144/172	46/58	7	0.18	0.67
OU 1	2012	China	Asian	CRC	HB	Taqman	331	713	159/289	135/312	37/112	6	3.23	0.07
OU 2	2012	China	Asian	GC	PB	Taqman	135	129	59/53	57/59	19/17	8	0.01	0.93
OU 3	2012	China	Asian	LC	PB	Taqman	105	107	43/44	46/49	16/14	7	0	0.95
Liu	2012	China	Asian	CRC	PB	Sequencing	467	456	189/165	222/227	56/64	7	1.01	0.32

*CRC colorectal cancer, BC breast cancer, PC prostate cancer, GC gastric cancer, LC liver cancer, PB population based, HB hospital based, PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism, NOS Newcastle-Ottawa Scale, HWE Hardy-Weinberg equilibrium

Table 2. Meta-analysis for the Association between ADIPOR1 rs1342387 Polymorphism and Risk of Cancer

Tumor type	Genetic model	OR (95%CI)	P_z	I^2%	P_h
Total	GG *vs* AA	1.22 (1.07-1.38)	0.003	31	0.152
	G *vs* A	1.13 (1.03-1.25)	0.01	52.7	0.02
	GG+GA *vs* AA	1.11 (1.00-1.24)	0.056	1.2	0.43
	GG *vs* GA+AA	1.20 (1.05-1.37)	0.006	46.5	0.044
CRC	GG *vs* AA	1.44 (1.21-1.70)	0	0	0.604
	G *vs* A	1.23 (1.11-1.36)	0	32.2	0.194
	GG+GA *vs* AA	1.28 (1.10-1.49)	0.002	0	0.908
	GG *vs* GA+AA	1.31 (1.12-1.55)	0.001	46.6	0.096
PC	GG *vs* AA	1.16 (0.86-1.58)	0.333	0	0.887
	G *vs* A	1.09 (0.93-1.27)	0.298	0	0.947
	GG+GA *vs* AA	1.08 (0.84-1.40)	0.543	0	0.44
	GG *vs* GA+AA	1.15 (0.89-1.47)	0.28	0	0.536
Other cancers (BC GC LC)	GG *vs* AA	0.86 (0.66-1.11)	0.241	0	0.915
	G *vs* A	0.93 (0.82-1.06)	0.293	0	0.814
	GG+GA *vs* AA	0.88 (0.72-1.08)	0.232	0	0.982
	GG *vs* GA+AA	0.95 (0.77-1.16)	0.593	0	0.732

p_z p value for Z test, I^2%the variation in OR attributable to heterogeneity, p_h p value of Q test for heterogeneity test, CRC colorectal cancer, BC breast cancer, PC prostate cancer, GC gastric cancer, LC liver cancer

significantly associated with risk of CRC in Asian ancestry for all genetic comparison models (GG *vs* AA, OR: 1.56, 95%CI: 1.26-1.92, p_z=0.000 Figure 2a; G carriers *vs* A carriers OR: 1.30, 95%CI: 1.18 -1.43, p_z=0.000 Figure 2b; Dominant model OR: 1.31, 95%CI: 1.08 -1.60, p_z=0.006

Table 3. Meta-analysis for the Association between ADIPOR1 rs1342387 Polymorphism and Risk of CRC by Ethnicity

Ethnicity	Genetic model	OR (95%CI)	P_z	I^2%	P_h
Caucasian or mixed (Caucasian mainly)					
	GG *vs* AA	1.21 (0.90-1.64)	0.208	0	0.335
	G *vs* A	1.10 (0.95-1.27)	0.224	8.6	0.296
	GG+GA *vs* AA	1.22 (0.95-1.57)	0.112	0	0.377
	GG *vs* GA+AA	1.05 (0.83-1.33)	0.668	0	0.469
Asian	GG *vs* AA	1.56 (1.26-1.92)	0	0	0.824
	G *vs* A	1.30 (1.18-1.43)	0	0	0.437
	GG+GA *vs* AA	1.31 (1.08-1.60)	0.006	0	0.9
	GG *vs* GA+AA	1.44 (1.26-1.64)	0	20.9	0.285

*p_z p value for Z test, I^2%the variation in OR attributable to heterogeneity, ph p value of Q test for heterogeneity test

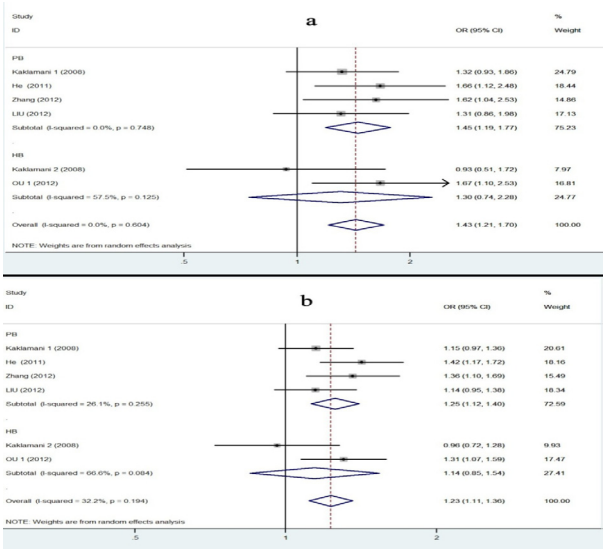

Figure 3. Forest Plots of Subgroup Analyses by Source of Controls for GG *vs* AA Model (A) and G Carriers *vs* A Carriers Model (B) with the Risk of CRC. A) In GG *vs* AA model, GG genotype of ADIPOR1 rs1342387 polymorphism significantly associated with increased risk of CRC compared with AA genotype for PB. Random-effect model was used. **B)** In G carriers *vs* A carriers model, G carriers of ADIPOR1 rs1342387 polymorphism significantly associated with increased risk of CRC compared with A carriers for PB. Random-effect model was used

Table 4. Meta-Analysis for the Association between ADIPOR1 rs1342387 Polymorphism and Risk of CRC by Source of Controls

Source of control	Genetic model	OR (95%CI)	P_z	I^2%	P_h
PB	GG *vs* AA	1.45 (1.19-1.77)	0	0	0.748
	G *vs* A	1.25 (1.12-1.40)	0	26.1	0.255
	GG+GA *vs* AA	1.28 (1.07-1.52)	0.007	0	0.988
	GG *vs* GA+AA	1.37 (1.12-1.67)	0.002	52.8	0.095
HB	GG *vs* AA	1.30 (0.75-2.28)	0.354	57.5	0.125
	G *vs* A	1.14 (0.85-1.54)	0.385	66.6	0.084
	GG+GA *vs* AA	1.29 (0.94-1.77)	0.114	29.3	0.234
	GG *vs* GA+AA	1.16 (0.80-1.69)	0.426	55.4	0.134

*p_z p value for Z test, I^2% the variation in OR attributable to heterogeneity, ph p value of Q test for heterogeneity test, PB population based, HB hospital based

Table 5. Begg's Test and Egger's Test for Assessing Publication Bias

Analyse	p value of Begg's test	p value of Egger's test
GG *vs* AA	0.707	0.379
G *vs* A	1	0.983
GG+GA *vs* AA	0.452	0.332
GG *vs* GA+AA	0.133	0.221

and Recessive model OR: 1.44, 95%CI: 1.26 -1.64, P_z =0.000), but not in Caucasian or mixed (Caucasian mainly) group (Table 3). When subgroup analyses were carried out by source of controls, significant relationships with risk of CRC were found in the subgroup of population-based studies in GG *vs* AA (OR: 1.45, 95%CI: 1.19-1.77, p_z=0.000) (Figure 3a), G carriers *vs* A carriers (OR: 1.25, 95%CI: 1.12 -1.40, p_z=0.000) (Figure 3b), Dominant model (OR: 1.28, 95%CI: 1.07 -1.52, p_z=0.007) and Recessive model (OR: 1.37, 95%CI: 1.12 -1.67, P_z =0.002) (Table 4).

Sensitivity analyses indicated that no independent study had influence the stability of pooled results about the relationship between polymorphism of rs1342387 and CRC. There was no publication bias for all genetic comparison models of CRC, and the results of the Beeg's and Egger's test were shown in Table 5.

Discussion

Obesity is an established risk factor for various types of cancers (Renehan et al., 2008), and recent studies had shown that adiponectin was a key player in the development and progression of obesity-related cancers (Barb et al., 2007; Paz-Filho et al., 2011). Adiponectin implemented the main biological function through its receptors, which were believed to be also expressed in many types of cancers (Dalamaga et al., 2012). Most recently, an increasing number of studies had shown that adiponectin receptor 1 genetic polymorphisms might be correlated with risk of cancer, and ADIPOR1 rs1342387 polymorphism had aroused great interest. Kaklamani VG et al. (2008) and He et al. (2011) had reported that rs1342387 polymorphism was correlated with the risk of colorectal cancer, while Beebe Dimmer et al. (2010) and Li Liu et al. (2011) did not observe this association. This contradiction might be due to small sample sizes or different ethnicities, and meta-analysis was a statistical technique for combining the results from independent studies to draw a more solid conclusion (Nordmann et al., 2012). So, this meta-analysis was carried out to assess the relationship between rs1342387polymorphism and risk of cancer. There had been several meta-analyses about the relationships between adiponectin gene polymorphism and risk of cancer (Fan et al., 2013; Xu et al., 2013; Yang et al., 2013; Zhou et al., 2013), but to the best of our knowledge, this was the first meta-analysis about the association between ADIPOR1gene (rs1342387) polymorphism and risk of cancer.

This meta-analysis suggested that ADIPOR1 rs1342387 polymorphism was associated with risk of cancer in GG *vs* AA, G carriers *vs* A carriers and Recessive

model. G carriers were associated with a 1.13-fold risk of cancer compared with A carriers.GG genotype of rs1342387 was associated with a 1.22-fold risk of cancer compared with AA genotype. The Finnish Diabetes Prevention Study shown that GG genotype of rs1342387 was associated with higher obesity measures than other genotypes (Siitonen et al., 2006). After reviewing several studies, Crimmins et al. (Crimmins and Martin, 2007) reported that rs1342387 was the only single nucleotide polymorphism (SNP) of adiponectin receptor 1 which was significantly associated with HOMA-IR as a measure of insulin resistance. Present studies had shown that obesity and insulin resistance were risk factors of kinds of cancers (Inoue and Tsugane, 2012; Vucenik and Stains, 2012). And Insulin levels were shown to be correlated with the expression of adiponectin receptors (Tsuchida et al., 2004), which could be downregulated by obesity and in turn lead to insulin resistance (Ouchi et al., 2000). So, the reason for G carriers and GG genotype of rs1342387 as a risk for cancer may be correlated to obesity and insulin resistance, which need to be further evaluated.

Stratified analyses were carried out to reduce heterogeneity and achieve a reliable result in the meta-analysis. In this study, a significant relationship was found in the subgroup of colorectal cancer for all genetic comparison models. G carriers were associated with a 1.23-fold risk of CRC compared with A carriers, and GG genotype of rs1342387 was associated with a 1.44-fold risk of CRC compared with AA genotype. Recently, a meta-analysis had suggested significantly inverse association between CRC and adiponectin level in prospective studies (OR=0.716, 95%CI: 0.606-0.847), which indicated that adiponectin may be involved in the development of CRC (Joshi and Lee, 2014). Polymorphisms of ADIPOR1 had been associated with the risk of colorectal cancer or colorectal adenoma, probably by affecting adiponectin plasma levels (He et al., 2011; An et al., 2012). However, Mather KJ et al. (2012) had reported that there was no relationship between ADIPOR1 rs1342387 and adiponectin concentrations. Kim AY et al. (Kim et al., 2010) reported that knockdown of ADIPOR1 could relieve the suppressive effect of adiponectin on the growth of colon cancer cells via AMP-activated protein kinase (AMPK) phosphorylation. The association of rs1342387 polymorphism with colorectal cancer risk maybe mainly due to affection of adiponectin function on cellular proliferation and apoptosis, and the direct relationship needs further study. Genotype frequency of various genetic polymorphisms may be different among people of different ethnicity. According to the data form Hapmap (http://snp.cshl.org/index.html.en), frequency of C allele was 54% for residents with Northern and Western European ancestry, and it was 62% for Han Chinese in Beijing. When subgroup analyses were conducted by ethnicity, ADIPOR1 rs1342387 polymorphism was significantly associated with risk of CRC among Asians for all genetic comparison models, however, no significant association was found in Caucasian or mixed (Caucasian mainly), which suggested that ethnic difference could influence the relationships between ADIPOR1 rs1342387and risk of CRC. But in the studies of Kaklamani et al. (Kaklamani et al., 2008), less than 3% participants were Asian ancestry, from which we couldn't extract the exact data of each genotype by race, and to some extent, this might affect the result of subgroup analyses by ethnicity. When stratified by whether the controls were population-based (PB) or hospital-based, more significantly association of rs1342387 with CRC risk was observed in PB studies. This might be because that controls of HB studies were suffering from certain diseases which might affect the results of analysis. After subgroup analyses were carried out by source of control, the heterogeneity of this meta-analysis was increased. So this result should be interpreted with caution.

In this meta-analysis, some limitations should be mentioned as well. Firstly, although we made great effort to search eligible studies, it was possible that few potential or unpublished studies might be missed. Secondly, the number of eligible studies and participants was relatively small for stratified analyses. There were only 2 studies for prostate cancer, 1 study for breast cancer, 1 study for gastric cancer and 1 study for liver cancer and we couldn't conduct the subgroup analyses by each cancer type. Similarly, the number of studies of hospital-based was small. Thirdly, when subgroup analyses were conducted by ethnicity in this meta-analysis, we couldn't extract the exact data of each genotype by race, and less than 3% participants in the studies of Kaklamani et al. (Kaklamani et al., 2008), which were Asian ancestry, were divided to Caucasian or mixed (Caucasian mainly) group. This might affect the result of subgroup analyses by ethnicity. And lastly, according to the data which had been collected, we couldn't conduct the combined analyses based on confounder adjustment.

In conclusion, this meta-analysis indicated that ADIPOR1 rs1342387 polymorphism was significantly associated with risk of colorectal cancer among Asian ancestry. More well-designed studies were required to confirm our conclusion in the future.

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