Three ADIPOR1 Polymorphisms and Cancer Risk: A Meta-Analysis of Case-Control Studies

Jiaxiang Ye1☯, Li Jiang2☯, Changliang Wu3*, Aiqun Liu1, Sufei Mao1, Lianying Ge1*  
1 Department of Medical Oncology, the Cancer Institute, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, Guangxi 530021, P.R. China,  
2 Graduate School of Guangxi Medical University, Nanning, Guangxi 530021, P.R. China,  
3 Department of Gastroenterology, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, P.R. China  
☯ These authors contributed equally to this work.  
* geliang1996@126.com; wuchangliang2013@126.com

Abstract

Background

Studies have come to conflicting conclusions about whether polymorphisms in the adiponectin receptor 1 gene (ADIPOR1) are associated with cancer risk. To help resolve this question, we meta-analyzed case-control studies in the literature.

Methods

PubMed, EMBASE, Cochrane Library, the Chinese Biological Medical Database and the Chinese National Knowledge Infrastructure Database were systematically searched to identify all case-control studies published through February 2015 examining any ADIPOR1 polymorphisms and risk of any type of cancer. Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated.

Results

A total of 13 case-control studies involving 5,750 cases and 6,762 controls were analyzed. Analysis of the entire study population revealed a significant association between rs1342387 (G/A) and overall cancer risk using a homozygous model (OR 0.82, 95%CI 0.72 to 0.94), heterozygous model (OR 0.84, 95%CI 0.76 to 0.93), dominant model (OR 0.85, 95%CI 0.75 to 0.97) and allele contrast model (OR 0.88, 95%CI 0.80 to 0.97). However, subgroup analysis showed that this association was significant only for Asians in the case of colorectal cancer. No significant associations were found between rs12733285(C/T) or rs7539542(C/G) and cancer risk, either in analyses of the entire study population or in analyses of subgroups.

Conclusions

Our meta-analysis suggests that the ADIPOR1 rs1342387(G/A) polymorphism, but not rs12733285(C/T) or rs7539542(C/G), may be associated with cancer risk, especially risk of colorectal cancer in Asians. Large, well-designed studies are needed to verify our findings.
Introduction

Cancer remains a frequent cause of death worldwide [1]. The prevalence of cancer around the world reflects, in part, the prevalence of obesity, which has been rising in parallel with living standards, not only in developed countries but also in some developing ones. Large epidemiological studies have revealed a significant association of obesity with various kinds of cancers, including colorectal, breast, endometrial, renal, esophageal, pancreatic, and biliary [2–4].

One link between obesity and cancer may be adiponectin, one of several cytokines secreted primarily by adipose tissue. Several studies suggest that adiponectin protects against obesity-related malignancy, such that higher serum levels are associated with lower risk of cancer [5–7]. Circulating adiponectin levels are influenced primarily by the activity of adiponectin receptors 1 and 2 (ADIPOR1, ADIPOR2) [8], and some studies have linked ADIPOR1 dysfunction with development of cancer [9, 10]. Exactly how the function or dysfunction of these receptors can lead to cancer remains poorly understood.

The ADIPOR1 gene has >28 single-nucleotide polymorphisms (SNPs) and two linkage disequilibrium blocks. Several of these polymorphisms have been associated with cancer risk, but studies have reported contrasting results depending on the cancer type or population involved. Some work has concluded that certain ADIPOR1 variants, including rs1342387(G/A), protect against colorectal cancer [11, 12], whereas a third study found that rs1342387(G/A) increases the risk of this cancer [13]. A case-control study reported that several ADIPOR1 SNPs were associated with prostate cancer risk [14], while two studies found no such association [10, 15]. One study showed no relationship between ADIPOR1 variants and breast cancer risk [16], whereas another study concluded that the SNP rs7539542 was associated with decreased breast cancer risk [17].

To help resolve these conflicting results using as large a sample as possible, we conducted a meta-analysis of case-control studies analyzing potential associations between various ADIPOR1 SNPs and risk of various types of cancer. We focused on the SNPs that have been studied most extensively: -1472C→T in intron 1 in linkage disequilibrium block 1 [rs12733285(C/T)], +5843G→A in intron 4 in block 1 [rs1342387(G/A)] and +10225 C→G in exon 8 in block 2 [rs7539542(C/G)].

Materials and Methods

Literature search

A comprehensive search was carried out using PubMed, EMBASE, Cochrane Library, the Chinese Biological Medical database and the Chinese National Knowledge Infrastructure database to identify case-control studies that were published through Feb.28, 2015 and that examined the association of ADIPOR1 polymorphisms with cancer risk. Searches were carried out using various combinations of customized terms and the MeSH-indexed terms “adiponectin”, “ADIPOR1”, “polymorphism”, and “cancer”, without restrictions on publication language. The following sequential search strategy was applied for each database: (#1)‘Adiponectin’: ab, ti OR ‘ADIPOQ’: ab, ti OR ‘Adiponectin’/exp OR ‘Adiponectin receptor 1’/exp; (#2)‘variation’: ab, ti OR ‘polymorphism’: ab, ti OR ‘SNP’: ab, ti OR ‘genetic polymorphism’/exp OR ‘genetic variability’/exp; (#3)‘neoplasm’: ab, ti OR ‘cancer’: ab, ti OR ‘carcinoma’: ab, ti OR ‘tumor’: ab, ti OR ‘neoplasm’/exp OR ‘carcinoma’/exp; (#4) #1 AND #2 AND #3. Search strings were adjusted accordingly for the other databases. References cited in identified articles were searched manually to find additional studies.
Study inclusion and exclusion

Inclusion and exclusion criteria were established before searching the literature. To be included in our meta-analysis, studies had to (1) apply a case-control design, (2) analyze the relationship between ADIPOR1 polymorphisms and cancer risk, and (3) report genotype data for cases and controls in sufficient detail for extracting and pooling with data from other studies. Studies were excluded if they were case reports, review articles or duplicate publications.

Data extraction

Two investigators (JXY, LJ) independently extracted the following data from included studies: first author’s name, year of publication, country/region and ethnicity of study population, type of cancer, source of controls (population- or hospital-based), genotyping method, number of case and control genotypes, and results of Hardy-Weinberg equilibrium (HWE) testing for genotype data from the control group. If HWE results were not reported, we determined them ourselves using a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). If other data were missing, we contacted study authors to request them.

Quality assessment

The quality of all eligible studies was evaluated using the Newcastle-Ottawa Scale (NOS), widely used for case-control studies [18]. The NOS provides a quality rating based on criteria covering three study dimensions: study group selection, comparability of cases and controls, and exposure of cases and controls. If all criteria are met, nine stars are rewarded. Seven stars are considered the cut-off for distinguishing “high-quality studies” from “low-quality studies”.

Statistical analysis

Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated using RevMan 5.1.0 (The Cochrane Collaboration, Oxford, UK) to assess the strength of associations of ADIPOR1 SNPs rs12733285(C/T), rs1342387(G/A) and rs7539542(C/G) with cancer risk. ORs were calculated using five genetic models: homozygous, heterozygous, dominant, recessive, and allele contrast. Subgroup analysis was also conducted according to ethnicity or cancer type. If only one study covering a particular cancer was included in the meta-analysis, we planned to categorize that study among those classified as dealing with “other” cancers.

Heterogeneity among studies was assessed using the Q-test and I² statistics. When heterogeneity was considered significant (P heterogeneity ≥ 0.1), a fixed-effect model was used; otherwise, a random-effect model was used (P heterogeneity < 0.1). Sensitivity analysis omitting one study at a time was also performed to confirm the main source of heterogeneity. Funnel plots were visually inspected for asymmetry to estimate the potential for publication bias [19]. In order to supplement funnel plot analysis, we performed Begg’s test [20] and Egger’s test [21] using Stata 12.0 (Stata Corporation, College Station, TX).

Results

Study selection and characteristics

This meta-analysis was conducted according to the recommendations of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement (S1 Checklist) and “Meta-analysis on Genetic Association Studies” statement (S2 Checklist). Systematic literature searches identified 10 publications [10–17, 22, 23] describing 13 case-control studies (Fig 1). One publication [13] described two case-control studies, and another [23] reported three case-control studies. Of the 13 studies, 10 analyzed the ADIPOR1 SNP rs12733285(C/T)
[10–14, 17, 23]; 12 analyzed rs1342387(G/A) [11–17, 22, 23]; and 8 analyzed rs7539542(C/G) [10, 13–17, 22] (Table 1). Genotype distribution in control groups was consistent with HWE in all 13 studies. All but two studies [15, 23] received at least seven stars on the NOS, indicating that they were high-quality (Table 1, S1 Table).

Quantitative synthesis

In pooled analysis using data from all 10 studies [10–14, 17, 23], no significant association was observed between the ADIPOR1 rs12733285C/T polymorphism and risk of any cancer, based on any of the five genetic models. Similar results were obtained in subgroup analyses (Table 2). A similar lack of association was observed for the SNP rs7539542(C/G) across all eight studies [10, 13–17, 22] and subgroups (Table 3, Fig 2).

In pooled analysis from all 12 studies [11–17, 22, 23], a significant association was observed between rs1342387(G/A) and cancer risk, according to four genetic models: homozygous (AA vs. GG, OR 0.82, 95%CI 0.72 to 0.94, $P_{\text{heterogeneity}} = 0.15$), heterozygous (AG vs. GG, OR 0.84, 95%CI 0.76 to 0.93, $P_{\text{heterogeneity}} = 0.10$), dominant (AA+AG vs. GG, OR 0.85, 95%CI 0.75 to 0.97, $P_{\text{heterogeneity}} = 0.02$) and allele contrast (A carriers vs. G carriers, OR 0.88, 95%CI 0.80 to 0.97, $P_{\text{heterogeneity}} = 0.02$) (Table 4, Figs 3–4).

The association between rs1342387(G/A) and cancer risk was checked in stratified analyses based on ethnicity (Table 4). The polymorphism was associated with decreased cancer risk in Asians according to all five genetic models: AA vs. GG, OR 0.68, 95%CI 0.56 to 0.83, $P_{\text{heterogeneity}} = 0.57$; AG vs. GG, OR 0.74, 95%CI 0.64 to 0.84, $P_{\text{heterogeneity}} = 0.34$; AA+AG vs. GG, OR 0.72, 95%CI 0.63 to 0.82, $P_{\text{heterogeneity}} = 0.28$; AA vs. AG+GG, OR 0.80, 95%CI 0.67 to 0.96, $P_{\text{heterogeneity}} = 0.77$; A carriers vs. G carriers, OR 0.79, 95%CI 0.72 to 0.87, $P_{\text{heterogeneity}} = 0.29$. However, no significant association was found in non-Asians.
### Table 1. Characteristics of studies included in the meta-analysis.

| Study              | Country | Ethnicity | Tumor type | Source of control | Genotyping method | Genotype data of case/control | HWE | NOS scores |
|--------------------|---------|-----------|------------|-------------------|-------------------|-------------------------------|------|------------|
| rs12733285C/T      |         |           |            |                   |                   |                               |      |            |
| Dhillon 2011[10]   | America | Non-Asian | PC         | PB                | MALDI-TOF         | 139/118, 547/528, 562/577    | Yes  | 9          |
| He 2011[11]        | China   | Asian     | CRC        | HB                | PCR-RFLP          | 0/0, 34/78, 386/477          | Yes  | 7          |
| Kaklamani 2008–1   | America | Non-Asian | CRC        | PB                | Taqman            | 69/105, 221/347, 147/200     | Yes  | 8          |
| Kaklamani 2008–2   | America | Non-Asian | CRC        | HB                | Taqman            | 19/14, 78/77, 98/101         | Yes  | 8          |
| Kaklamani 2008–3   | America | Non-Asian | BC         | PB                | Taqman            | 100/126, 294/315, 321/366   | Yes  | 7          |
| Kaklamani 2011[14] | America | Non-Asian | PC         | PB                | Taqman            | 48/71, 221/222, 183/145      | Yes  | 8          |
| Ou 2012–1[23]      | China   | Asian     | CRC        | HB                | Taqman            | 2/7, 47/93, 289/614         | Yes  | 6          |
| Ou 2012–2[23]      | China   | Asian     | GC         | PB                | Taqman            | 0/0, 19/15, 113/121         | Yes  | 8          |
| Ou 2012–3[23]      | China   | Asian     | HC         | PB                | Taqman            | 0/0, 12/14, 94/94           | Yes  | 8          |
| Zhang 2012[12]     | China   | Asian     | CRC        | HB                | PCR-RFLP          | 0/0, 30/50, 340/320         | Yes  | 7          |
| rs1342387G/A       |         |           |            |                   |                   |                               |      |            |
| Beebe-Dimmer 2010  | America | Non-Asian | PC         | PB                | Taqman            | 31/74, 59/172, 41/87        | Yes  | 6          |
| He 2011[11]        | China   | Asian     | CRC        | HB                | PCR-RFLP          | 50/82, 157/263, 213/210     | Yes  | 7          |
| Kaklamani 2008–1   | America | Non-Asian | CRC        | PB                | Taqman            | 99/179, 223/313, 113/155    | Yes  | 8          |
| Kaklamani 2008–2   | America | Non-Asian | CRC        | HB                | Taqman            | 32/32, 101/99, 57/61        | Yes  | 8          |
| Kaklamani 2008–3   | America | Non-Asian | BC         | PB                | Taqman            | 201/209, 362/419, 145/180   | Yes  | 7          |
| Kaklamani 2011[14] | America | Non-Asian | PC         | PB                | Taqman            | 112/122, 218/209, 116107    | Yes  | 8          |
| Liu 2011[22]       | China   | Asian     | CRC        | HB                | MALDI-TOF         | 56/64, 222/227, 189/165     | Yes  | 7          |
| Ou 2012–1[23]      | China   | Asian     | CRC        | HB                | Taqman            | 37/112, 135/312, 159/289    | Yes  | 6          |
| Ou 2012–2[23]      | China   | Asian     | GC         | PB                | Taqman            | 19/17, 57/59, 59/53         | Yes  | 8          |
| Ou 2012–3[23]      | China   | Asian     | HC         | PB                | Taqman            | 16/14, 46/49, 43/44         | Yes  | 8          |
| Teras 2009[16]     | America | Non-Asian | BC         | PB                | Sequencing        | 458/457, 172/184            | Yes  | 8          |
| Zhang 2012[12]     | China   | Asian     | CRC        | HB                | PCR-RFLP          | 46/58, 144/172, 180/140     | Yes  | 7          |
| rs7539542C/G       |         |           |            |                   |                   |                               |      |            |
| Beebe-Dimmer 2010  | America | Non-Asian | PC         | PB                | Taqman            | 54/140, 56/133, 19/49       | Yes  | 6          |
| Dhillon 2011[10]   | America | Non-Asian | PC         | PB                | MALDI-TOF         | 538/543, 513/489, 135/135   | Yes  | 9          |
| Kaklamani 2008–1   | America | Non-Asian | CRC        | PB                | Taqman            | 44/63, 209/280, 179/306     | Yes  | 8          |
| Kaklamani 2008–2   | America | Non-Asian | CRC        | HB                | Taqman            | 26/24, 75/81, 96/89        | Yes  | 8          |

(Continued)
Next, the association between rs1342387(G/A) and cancer risk was checked in stratified analyses based on cancer type (Table 4). The SNP was significantly associated with decreased risk of colorectal cancer, according to all five genetic models: AA vs. GG, OR 0.70, 95%CI 0.59 to 0.83, P heterogeneity = 0.60; AG vs. GG, OR 0.79, 95%CI 0.66 to 0.94, P heterogeneity = 0.07; AA+AG vs. GG, OR 0.75, 95%CI 0.67 to 0.84, P heterogeneity = 0.10; AA vs. AG+GG, OR 0.78, 95%CI 0.67 to 0.84, P heterogeneity = 0.91; A carriers vs. G carriers, OR 0.81, 95%CI 0.75 to 0.88, P heterogeneity = 0.19. However, no significant association was observed for prostate or other cancers.

Besides, the association between rs1342387(G/A) and cancer risk in Asians was also checked in stratified analyses based on cancer type (Table 5). The SNP was significantly associated with decreased risk of colorectal cancer in Asians, according to all five genetic models: AA vs. GG, OR 0.64, 95%CI 0.52 to 0.79, P heterogeneity = 0.82; AG vs. GG, OR 0.71, 95%CI 0.62 to 0.82, P heterogeneity = 0.23; AA+AG vs. GG, OR 0.70, 95%CI 0.61 to 0.80, P heterogeneity = 0.28; AA vs. AG+GG, OR 0.76, 95%CI 0.63 to 0.93, P heterogeneity = 0.90; A carriers vs. G carriers, OR 0.77, 95%CI 0.69 to 0.86, P heterogeneity = 0.03. However, no significant association was observed for prostate or other cancers.

Table 2. Overall and subgroup analysis of the ADIPOR1 rs12733285(C/T) polymorphism and cancer risk.

| Variable | Homozygous model | Heterozygous model | Dominant model | Recessive model | Allele contrast model |
|----------|------------------|--------------------|----------------|-----------------|----------------------|
|          | OR [95%CI] | P² | OR [95%CI] | P² | OR [95%CI] | P² | OR [95%CI] | P² | OR [95%CI] | P² |
| Total    | 0.91[0.69,1.19] | 0.04 | 0.90[0.77,1.05] | 0.04 | 0.89[0.76,1.04] | 0.01 | 0.95[0.82,1.10] | 0.11 | 0.91[0.80,1.04] | <0.1 |
| Ethnicity |                   |          |                   |          |                   |          |                   |          |                   |          |
| Non-Asian | 0.92[0.69,1.22] | 0.02 | 0.99[0.89,1.10] | 0.34 | 0.98[0.89,1.09] | 0.11 | 0.94[0.75,1.19] | 0.07 | 0.96[0.85,1.09] | 0.03 |
| Asian    | 0.61[0.13,2.94] | NA | 0.79[0.55,1.14] | 0.05 | 0.79[0.55,1.12] | 0.05 | 0.60[0.12,2.91] | NA | 0.79[0.57,1.09] | 0.08 |
| Tumor type |                   |          |                   |          |                   |          |                   |          |                   |          |
| CRC      | 0.96[0.69,1.32] | 0.48 | 0.80[0.61,1.04] | 0.05 | 0.81[0.62,1.05] | 0.04 | 1.01[0.76,1.36] | 0.56 | 0.84[0.67,1.07] | 0.03 |
| PC       | 0.82[0.37,1.82] | <0.1 | 0.94[0.70,1.25] | 0.08 | 0.90[0.61,1.34] | 0.01 | 0.86[0.46,1.63] | <0.1 | 0.92[0.65,1.30] | <0.1 |
| Others   | 0.90[0.67,1.22] | NA | 1.07[0.87,1.31] | 0.71 | 0.89[0.63,1.26] | 0.11 | 0.88[0.66,1.17] | NA | 0.98[0.85,1.14] | 0.66 |

Notes: CI, confidence interval; CRC, colorectal cancer; NA, not available; OR, odds ratio; PC, prostate cancer.

PLOS ONE | DOI:10.1371/journal.pone.0127253 June 5, 2015 6/14
95%CI 0.70 to 0.85, $P_{\text{heterogeneity}} = 0.44$, but no significant association was observed for other cancers.

### Sensitivity analysis

Sensitivity analysis was performed to confirm the main source of heterogeneity across studies. Data for rs12733285(C/T) pooled from all studies showed significant heterogeneity in all genetic models except the recessive model (Table 2). Sensitivity analysis identified the primary sources of heterogeneity to be Kaklamani et al. [14] in the homozygous model, He et al. [11] in the heterozygous model, and He et al. [11] and Zhang et al. [12] in both the dominant and allele contrast models. Removing these studies did not significantly alter the results: TT vs. CC, OR 1.03, 95%CI 0.87 to 1.22, $P_{\text{heterogeneity}} = 0.45$; CT vs. CC, OR 0.97, 95%CI 0.88 to 1.07, $P_{\text{heterogeneity}} = 0.22$; TT + CT vs. CC, OR 0.99, 95%CI 0.90 to 1.09, $P_{\text{heterogeneity}} = 0.29$ (Fig 5); A carriers vs. G carriers, OR 0.98, 95%CI 0.92 to 1.06, $P_{\text{heterogeneity}} = 0.12$.

Data for rs1342387(G/A) pooled from all studies showed significant heterogeneity in the dominant model, due primarily to He et al. [11], as well as in the allele contrast model, due primarily to Kaklamani et al. [13]. Omitting these studies did not influence the results in the allele contrast model (T carriers vs. G carriers, OR 0.84, 95%CI 0.79 to 0.90, $P_{\text{heterogeneity}} = 0.26$) (Fig 6), although it did uncover a borderline association in the dominant model (AA + AG vs. GG, OR 0.89, 95%CI 0.80 to 1.00, $P_{\text{heterogeneity}} = 0.18$).

### Table 3. Overall and subgroup analysis of the ADIPOR1 rs7539542(C/G) polymorphism and cancer risk.

| Variable | Homozygous model | Heterozygous model | Dominant model | Recessive model | Allele contrast model |
|----------|------------------|--------------------|----------------|----------------|----------------------|
|          | OR [95%CI]       | P                  | OR [95%CI]     | P              | OR [95%CI]           | P              |
| Total    | 1.02[0.88,1.18]  | 0.66               | 1.05[0.94,1.18]| 0.27           | 1.05[0.95,1.16]      | 0.43           |
| Ethnicity|                  |                    |                |                |                      | 1.00[0.91,1.08] | 0.49 |
| Non-Asian| 1.07[0.91,1.25]  | 0.95               | 1.08[0.96,1.22]| 0.43           | 1.08[0.97,1.19]      | 0.72           |
| Asian    | 0.74[0.49,1.09]  | NA                 | 0.77[0.53,1.14]| NA             | 0.76[0.52,1.09]      | NA             |
| Tumor type|                 |                  |                |                |                      | 1.00[0.96,1.11] | 0.72 |
| CRC      | 0.93[0.72,1.21]  | 0.26               | 0.97[0.70,1.36]| 0.06           | 0.97[0.70,1.35]      | 0.05           |
| PC       | 1.00[0.80,1.24]  | 1.00               | 1.13[0.94,1.36]| 0.69           | 1.09[0.92,1.30]      | 0.68           |
| Others   | 1.19[0.88,1.61]  | NA                 | 0.96[0.77,1.19]| NA             | 1.03[0.89,1.20]      | 0.80           |

Notes: CI, confidence interval; CRC, colorectal cancer; NA not available; OR, odds ratio; PC, prostate cancer. $^a$ P value of Q test for assessing heterogeneity.

doi:10.1371/journal.pone.0127253.t003

Fig 2. Forest plot of the association between ADIPOR1 SNP rs7539542(C/G) and cancer risk in a dominant model.

doi:10.1371/journal.pone.0127253.g002
**Publication bias**

Visual inspection of the funnel plots (Figs 7–9) suggested a roughly symmetrical distribution for the studies covering each of the ADIPOR1 SNPs according to the dominant model, indicating low risk of publication bias in the meta-analysis. Similarly, Egger’s and Begg’s tests revealed no significant potential for publication bias under the dominant model: rs12733285(C/T), \( P_{\text{Begg}} = 0.325 \) and \( P_{\text{Egger}} = 0.252 \); rs1342387(G/A), \( P_{\text{Begg}} = 0.784 \) and \( P_{\text{Egger}} = 0.785 \); and rs7539542(C/G), \( P_{\text{Begg}} = 0.621 \) and \( P_{\text{Egger}} = 0.368 \).

**Discussion**

ADIPOR1, expressed at high levels in skeletal muscle and pancreatic beta cells [24–26], is expressed in many types of cancer, including breast, colorectal, pancreatic, and esophageal cancers [27–30]. Despite numerous studies of the possible association of ADIPOR1 SNPs rs12733285(C/T), rs1342387(G/A) and rs7539542(C/G) with cancer risk [10–17, 22, 23], whether these polymorphisms are indeed associated with cancer risk remains unclear. Combining the statistical power of 13 case-control studies in this meta-analysis, we show that the A allele of ADIPOR1 rs1342387 is associated with significantly lower risk of colorectal cancer.
than is the G allele in Asians, suggesting that the A allele may protect against such cancer in this ethnic group. This SNP does not appear to be associated with risk of other cancers in Asians, or with risk of any cancers in non-Asians. The SNPs rs12733285(C/T) and rs7539542 (C/G) did not show significant associations with any type of cancer in meta-analyses involving all data or data from subgroups.

To verify the reliability of our meta-analyses, we performed sensitivity analyses when significant heterogeneity was present across pooled studies. Removing the studies that explained most of this heterogeneity did not significantly alter the initial results, confirming their reliability. We also sought to reduce publication bias by searching not only in Western databases of research literature but also in the major Chinese ones. Studies have shown that for some areas of genetic epidemiology, Chinese-language journals not indexed in PubMed contain a higher proportion of articles reporting nonsignificant results than do PubMed-indexed journals [31], so combining Western and Chinese databases may help us to reduce selective reporting bias.

Our results suggesting that the A allele of rs1342387(G/A) protects against colorectal cancer at least in Asians is consistent with a previous report that the A allele is associated with higher serum levels of adiponectin [32], and serum adiponectin levels are inversely associated with risk of obesity-related malignancies [5–7]. One study reported an association of rs1342387(G/A) with increased colorectal cancer risk in a single Caucasian population using the dominant model [13], but the association disappeared upon re-analysis using a Cockerham model [33]. Similarly, logistic regression analysis of 7,020 cases and 7,631 controls of European descent

Fig 4. Forest plot of the association between ADIPOR1 SNP rs1342387(G/A) and cancer risk in a heterozygous model.

doi:10.1371/journal.pone.0127253.g004

Table 5. Overall and subgroup analysis of the ADIPOR1 rs1342387(G/A) polymorphism and cancer risk in Asians.

| Variable    | Homozygous model | Heterozygous model | Dominant model | Recessive model | Allele contrast model |
|-------------|------------------|-------------------|----------------|-----------------|---------------------|
| OR [95%CI]  | P                | OR [95%CI]        | P              | OR [95%CI]      | P                   |
| Total       | 0.68[0.56,0.83]  | 0.57              | 0.74[0.64,0.84]| 0.34            | 0.72[0.63,0.82]     | 0.28                | 0.80[0.67,0.96]     | 0.77                | 0.79[0.72,0.87]     | 0.29                |
| Tumor type  |                  |                   |                |                 |                     |                     |
| CRC         | 0.64[0.52,0.79]  | 0.82              | 0.71[0.62,0.82]| 0.23            | 0.70[0.61,0.80]     | 0.28                | 0.76[0.63,0.93]     | 0.90                | 0.77[0.70,0.85]     | 0.44                |
| Others      | 1.08[0.62,1.88]  | 0.79              | 0.91[0.62,1.34]| 0.80            | 0.94[0.66,1.36]     | 0.76                | 1.13[0.67,1.90]     | 0.85                | 1.00[0.77,1.31]     | 0.75                |

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

P values of Q test for assessing heterogeneity.

Bold values indicate significant associations.

doi:10.1371/journal.pone.0127253.t005
failed to find an association between rs1342387(G/A) and risk of colorectal cancer [34]. That these studies failed to detect an association reflects the diverse effects of ADIPOR1 variants in Caucasians, consistent with the present study. ADIPOR1 and ADIPOR2 mediate the link between adiponectin and activation of AMP-activated protein kinase, which causes adiponectin to exert anti-proliferative effects under cancer conditions [8]. The ADIPOR1 SNP rs1342387(G/A) may modulate the effects of adiponectin on cancer risk by regulating the expression of adiponectin receptors, but our results suggest that this is not necessarily true in all cancers and all ethnicities. This may help explain conflicting reports in the literature about the association of this SNP with cancer risk.

Our findings that the A allele of rs1342387 protects against colorectal cancer in Asians and that rs12733285(C/T) shows no significant associations with colorectal cancer risk were also reported in a meta-analysis by Ou et al. [23]. The present work extends that study in several important ways. First, we included a larger number of colorectal cancer patients than Ou et al. Second, we performed subgroup analyses based on ethnicity and cancer type, while Ou et al. did not. Our findings are therefore a critical contribution to the literature because they provide strong evidence that the same ADIPOR1 SNP can exert more or less influence on cancer risk depending on the type of cancer and ethnicity. Third, we examined associations between the SNPs and cancer risk using five genetic models, whereas Ou et al. reported results using only the dominant model.

Similar to the present meta-analysis, Yu et al. reported in their meta-analysis that the SNP rs1342387(G/A) is associated with colorectal cancer risk in Asians [35]. Our study extends
Fig 7. Funnel plot to detect publication bias in data on ADIPOR1 SNP rs12733285(C/T) according to a dominant model.
doi:10.1371/journal.pone.0127253.g007

Fig 8. Funnel plot to detect publication bias in data on ADIPOR1 SNP rs1342387(G/A) according to a dominant model.
doi:10.1371/journal.pone.0127253.g008

Fig 9. Funnel plot to detect publication bias in data on ADIPOR1 SNP rs7539542(C/G) according to a dominant model.
doi:10.1371/journal.pone.0127253.g009
those findings, because Yu et al. did not use as large a sample size as we did, nor did they examine relationships between rs12733285(C/T) or rs7539542(C/G) and risk of cancer. In addition, Yu et al. did not check the association between rs1342387(G/A) and cancer risk in Asians based on stratified analyses.

Despite its strengths, our meta-analysis has several limitations. First, it focused only on SNPs, but numerous factors act individually and together to influence risk of cancer, including lifestyle, dietary habits, environment, and genetics. The included studies in our meta-analysis reported data on few or none of these issues, making it impossible for us to assess them across patients and controls. Second, since various types of cancer were included, the patient and control populations were heterogeneous. The different sources of controls (population- or hospital-based) might create selection bias toward the null hypothesis. Third, the meta-analysis included a relatively small number of studies and did not take into account unpublished data or “grey literature”. This may raise the risk of publication bias, even though our analyses suggest the absence of significant risk.

In conclusion, our meta-analysis suggests that the ADIPOR1 SNP rs1342387(G/A), but not the SNPs rs12733285(C/T) or rs7539542(C/G), are associated with cancer risk, especially risk of colorectal cancer in Asians. Large, well-designed studies are needed to verify and extend our findings.

Supporting Information
S1 Checklist. PRISMA 2009 checklist.
(DOC)

S2 Checklist. Meta-analysis of Genetic Association Studies checklist.
(DOC)

S1 Appendix. The 21 excluded articles and the reasons.
(DOC)

S1 Table. Results of quality assessment using the Newcastle–Ottawa Scale for case-control studies.
(DOC)

Author Contributions
Conceived and designed the experiments: LYG CLW JXY. Performed the experiments: JXY LJ AQL. Analyzed the data: JXY LJ SFM. Contributed reagents/materials/analysis tools: JXY LJ AQL. Wrote the paper: JXY LJ LYG.

References
1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61(2):69–90. Epub 2011/02/08. doi:10.3322/caac.20107 PMID: 21296855.
2. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348(17):1625–38. Epub 2003/04/25. doi:10.1056/NEJMoa021423 PMID: 12711737.
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008; 371(9612):569–78. Epub 2008/02/19. doi: 10.1016/s0140-6736(08)60269-x PMID: 18280327.
4. Wolk A, Gridley G, Svensson M, Nyren O, McLaughlin JK, Fraumeni JF, et al. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control. 2001; 12(1):13–21. Epub 2001/03/03. PMID: 11227921.
5. An W, Bai Y, Deng SX, Gao J, Ben QW, Cai QC, et al. Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis. Eur J Cancer Prev. 2012; 21(2):126–33. Epub 2011/10/01. doi: 10.1097/CNJ.0b013e32834c9055 PMID: 21960184.

6. Wu MM, Chen HC, Chen CL, You SL, Cheng WF, Chen CA, et al. A prospective study of gynecological cancer risk in relation to adiposity factors: cumulative incidence and association with plasma adipokine levels. PLoS One. 2014; 9(8):e104630. Epub 2014/08/15. doi: 10.1371/journal.pone.0104630 PMID: 25115836.

7. Ye J, Jia J, Dong S, Zhang C, Yu S, Li L, et al. Circulating adiponectin levels and the risk of breast cancer: a meta-analysis. Eur J Cancer Prev. 2014; 23(3):158–65. Epub 2013/08/10. doi: 10.1097/CEJ.0b013e328364f293 PMID: 23929213.

8. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang SH, et al. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol. 2010; 24(7):1441–52. Epub 2010/05/07. doi: 10.1210/me.2009-0498 PMID: 20448885.

9. Cohen SS, Gammon MD, North KE, Millikan RC, Lange EM, Williams SM, et al. ADIPOQ, ADIPOR1, and ADIPOR2 polymorphisms in relation to serum adiponectin levels and BMI in black and white women. Obesity (Silver Spring). 2011; 19(10):2053–62. Epub 2011/01/29. doi: 10.1038/oby.2010.346 PMID: 21739922.

10. Dhillon PK, Penney KL, Schumacher F, Rider JR, Sesso HD, Pollak M, et al. Common polymorphisms in the adiponectin and its receptor genes, adiponectin levels and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2011; 20(12):2618–27. Epub 2011/10/01. doi: 10.1158/1055-9965.epi-11-0434 PMID: 21960694.

11. He B, Pan Y, Zhang Y, Bao Q, Chen L, Nie Z, et al. Effects of genetic variations in the adiponectin pathway genes on the risk of colorectal cancer in the Chinese population. BMC Med Genet. 2011; 12(1):94–100. Epub 2011/07/14. doi: 10.1186/1471-2390-12-94 PMID: 21749709.

12. Zhang Y, Feng QL, Liu CM, Di RK. Relationship between polymorphism sites of adiponectin and its receptor gene and the susceptibility of colorectal cancer. Journal of Jiangsu University. 2012; 22(4):336–41.

13. Kaklamani VG, Wisinski KB, Sadim M, Gulden C, Do A, Offit K, et al. Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. JAMA. 2008; 300(13):1523–31. Epub 2008/10/02. doi: 10.1001/jama.300.13.1523 PMID: 18827209.

14. Kaklamani V, Yi N, Zhang K, Sadim M, Offit K, Oddoux C, et al. Polymorphisms of ADIPOQ and ADIPOR1 and prostate cancer risk. Metabolism. 2011; 60(9):1234–43. Epub 2011/03/15. doi: 10.1016/j.metabol.2011.01.003 PMID: 21397927.

15. Beebe-Dimmer JL, Zuhlke KA, Ray AM, Lange EM, Cooney KA. Genetic variation in adiponectin (ADIPOQ) and the type 1 receptor (ADIPOR1), obesity and prostate cancer in African Americans. Prostate Cancer Prostatic Dis. 2010; 13(4):362–7. Epub 2010/04/03. doi: 10.1038/pcan.2010.27 PMID: 20697428.

16. Teras LR, Goodman M, Patel AV, Bouzyk M, Tang W, Diver WR, et al. No association between polymorphisms in LEP, LEPR, ADIPOQ, ADIPOR1, or ADIPOR2 and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2009; 18(9):2553–7. Epub 2009/05/04. doi: 10.1158/1055-9965.epi-09-0542 PMID: 19723917.

17. Kaklamani VG, Sadim M, Hsi A, Offit K, Oddoux C, Ostrer H, et al. Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. Cancer Res. 2008; 68(9):3178–84. Epub 2008/05/03. doi: 10.1158/0008-5472.can-07-0533 PMID: 18451143.

18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of non-randomized studies in meta-analyses. Eur J Epidemiol. 2010; 25(9):603–5. Epub 2010/07/24. doi: 10.1007/s10654-010-9491-z PMID: 20652370.

19. Bennett DA, Latham NK, Stretton C, Anderson CS. Capture-recapture is a potentially useful method for assessing publication bias. J Clin Epidemiol. 2004; 57(4):349–57. Epub 2004/05/12. doi: 10.1016/j.jclinepi.2003.09.015 PMID: 15135835.

20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):1088–101. Epub 1994/12/01. PMID: 7786990.

21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629. Epub 1997/10/06. PMID: 9310563.

22. Liu L, Zhong R, Wei S, Yin JY, Xiang H, Zou L, et al. Interactions between genetic variants in the adiponectin, adiponectin receptor 1 and environmental factors on the risk of colorectal cancer. PLoS One. 2011; 6(11):e27301. Epub 2011/11/17. doi: 10.1371/journal.pone.0027301 PMID: 22087284.

23. Ou YY. The association of polymorphisms on ADIPOQ and ADIPOR1 with risk and prognosis of cancer. Ph.D. Thesis, The Second Military Medical University. 2012. Available: http://epub.cnki.net/kns/brief/default_result.aspx. Accessed 26 July 2014.
24. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev. 2005; 26(3):439–51. Epub 2005/05/18. doi: 10.1210/er.2005-0005 PMID: 15897298.

25. Kharrour I, Rasschaert J, Eizirik DL, Crop M. Expression of adiponectin receptors in pancreatic beta cells. Biochem Biophys Res Commun. 2003; 312(4):1118–22. Epub 2003/12/04. PMID: 14651988.

26. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate anti-diabetic metabolic effects. Nature. 2003; 423(6941):762–9. Epub 2003/06/13. doi: 10.1038/nature01705 PMID: 12802337.

27. Dalamaga M, Migdalis I, Fargnoli JL, Papadavid E, Bloom E, Mitsiades N, et al. Pancreatic cancer expresses adiponectin receptors and is associated with hypoleptinemia and hyperadiponectinemia: a case-control study. Cancer Causes Control. 2009; 20(5):625–33. Epub 2008/12/04. doi: 10.1007/s10552-008-9273-z PMID: 19051043.

28. Komer A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, et al. Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. J Clin Endocrinol Metab. 2007; 92(3):1041–8. Epub 2006/12/29. doi: 10.1210/jc.2006-1858 PMID: 17192291.

29. Ogunwobi OO, Beales IL. Globular adiponectin, acting via adiponectin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. Mol Cell Endocrinol. 2008; 285(1–2):43–50. Epub 2008/03/04. doi: 10.1016/j.mce.2008.01.023 PMID: 18313838.

30. Williams CJ, Mitsiades N, Sozopoulos E, Hsi A, Wolff A, Nifli AP, et al. Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. Endocr Relat Cancer. 2008; 15(1):289–99. Epub 2008/03/04. doi: 10.1677/erc-07-0197 PMID: 18310295.

31. Pan Z, Trikalinos TA, Kavvoura FK, Lau J, Ioannidis JP. Local literature bias in genetic epidemiology: an empirical evaluation of the Chinese literature. PLoS Med. 2005; 2(12):e334. Epub 2005/11/16. doi: 10.1371/journal.pmed.0020334 PMID: 16285839.

32. Heid IM, Wagner SA, Gohlke H, Iglseder B, Mueller JC, Cip P, et al. Genetic architecture of the APM1 gene and its influence on adiponectin plasma levels and parameters of the metabolic syndrome in 1,727 healthy Caucasians. Diabetes. 2006; 55(2):375–84. Epub 2006/01/31. PMID: 16443770.

33. Yi N, Kaklamani VG, Pasche B. Bayesian analysis of genetic interactions in case-control studies, with application to adiponectin genes and colorectal cancer risk. Ann Hum Genet. 2011; 75(1):90–104. Epub 2010/09/18. doi: 10.1111/j.1469-1809.2010.00605.x PMID: 20846215.

34. Song M, Gong J, Giovannucci EL, Berndt SI, Brenner H, Chang-Claude J, et al. Genetic variants of adiponectin and risk of colorectal cancer. Int J Cancer. 2014; Epub 2014/11/29. doi: 10.1002/ijc.29360 PMID: 25431318.

35. Yu LX, Zhou NN, Liu LY, Wang F, Ma ZB, Li J, et al. Adiponectin Receptor 1 (ADIPOR1) rs1342387 Polymorphism and Risk of Cancer: a Meta-analysis. Asian Pac J Cancer Prev. 2014; 15(18):7515–20. Epub 2014/10/09. PMID: 25292021.