Adiponectin levels in patients with colorectal cancer and adenoma: a meta-analysis

Wei An, Yu Bai, Shang-Xin Deng, Jie Gao, Qi-Wen Ben, Quan-Cai Cai, Hua-Gao Zhang and Zhao-Shen Li

Inconsistent results with regard to adiponectin levels in patients with colorectal cancer (CRC) and adenoma have been reported. To evaluate adiponectin levels in patients with CRC and adenoma, a meta-analysis on studies which compared adiponectin levels in patients with CRC or adenoma with healthy controls was carried out. A literature search was performed through Pubmed, EMBASE, and Science Citation Index Expanded database. Pooled-weighted mean differences and 95% confidence intervals (95%CI) were calculated by using random-effects models. Heterogeneity between studies was assessed using the Cochran's *Q* and I^2 statistics. A total of 13 studies were identified, which included 2632 cases of CRC or adenoma and 2753 healthy controls. Adiponectin levels were significantly lower in patients with CRC or adenoma compared with healthy controls, with significant heterogeneity [weighted mean differences of −1.51 (95% CI: −2.42 to −0.59; $P_{heterogeneity}<0.001$) for CRC and −1.29 (95% CI: −2.01to −0.58; $P_{heterogeneity}<0.001$) for colorectal adenoma, respectively]. On stratified analysis of CRC, significant difference in adiponectin levels between patients with CRC and healthy controls was reported only in case–control studies or small sample size studies ($n<100$), but not in nested case–control studies or large sample size studies ($n \geq 100$). In addition, metaregression analysis indicated that study design and sample size partly contributed to the significant heterogeneity ($P=0.022$ for study design and $P=0.018$ for sample size, respectively). For colorectal adenoma studies, stratified analysis indicated that sample size was one of the heterogeneous factors. Sensitivity analysis showed that there were no changes in the direction of effect when any one study was excluded. No publication bias was detected. Adiponectin levels are lower in patients with CRC or colorectal adenoma compared with those in healthy controls. Future studies are warranted to clarify the association of adiponectin levels and carcinogenesis of the colorectum. ***European Journal of Cancer Prevention*** **21:126–133 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Obesity, hyperinsulinemia, and insulin resistance (IR) have been consistently considered as important risk factors for the development of colorectal cancer (CRC) and adenoma (Giovannucci, 1995; Bianchini *et al.*, 2002), which is a precursor lesion of CRC. Previous reviews have indicated that obesity is associated with a 7–60% increase in the risk of CRC (Bergstrom *et al.*, 2001; Dai *et al.*, 2007; Larsson and Wolk, 2007), and meta-analyses of insulin concentration and cancer have strongly supported a relationship between hyperinsulinemia and an increased risk of colon and rectal cancer (Pisani, 2008). However, the mechanisms underlying this association between obesity or IR and colorectal tumor development have not been fully elucidated (Komninou *et al.*, 2003; Jee *et al.*, 2005; Osório-Costa *et al.*, 2009).

Adiponectin, a 30-kDa complement C1-related protein, is principally secreted by adipocytes (Nishida *et al.*, 2007). It can stimulate insulin secretion, as well as increases fatty acid combustion and energy consumption (Kadowaki *et al.*, 2006). Several studies have found that levels of adiponectin are inversely correlated with IR and obesity, especially abdominal obesity (Nakashima *et al.*, 2006; Hanley *et al.*, 2007). Therefore, low levels of adiponectin may provide a link between obesity, IR, and the risk of CRC. A prospective study (Wei *et al.*, 2005) has demonstrated that elevated adiponectin levels are associated with a reduced risk of CRC, independent of BMI, waist circumference, and waist-to-hip ratio. Several case–control studies (Otake *et al.*, 2005, 2010; Guadagni *et al.*, 2009; Gonullu *et al.*, 2010; Kemik *et al.*, 2010) have obtained similar results and found that adiponectin levels in patients with CRC or adenoma were lower than those in healthy controls. However, inconsistent results regarding this have been reported in other studies (Lukanova *et al.*, 2006; Fukumoto *et al.*, 2008; Stocks *et al.*, 2008). Understanding the association between circulating concentrations of adiponectin and CRC or adenoma may

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provide useful information on the diseases; however, currently, no study has systematically summarized the existing evidence.

The aim of this study is to summarize the current state of evidence on the adiponectin level in patients with CRC or adenoma under special consideration of the possible heterogeneity in the included literature.

Methods

Search strategy

We performed a systematic literature search of Pubmed (MEDLINE), EMBASE, and Science Citation Index Expanded (Institute for Scientific Information Web of Science) databases for relevant published reports from the beginning of indexing for each database to 15 December 2010. The search strategy used the following terms: adiponectin, adipoq, acdc, ACRP30, APM1, GBP28, c1q collagen domain-containing protein, 30-kda adipocyte complement-related protein, or adipose most abundant gene transcript 1; colorectal, colon, or rectum; and cancer, carcinoma, neoplasia, tumor, neoplasm, adenoma, or adenomatous polyps. No language restriction was imposed. We also checked the reference list of relevant reviews and original articles to identify additional studies.

Study selection

Screening of titles, abstracts, and full-text articles, as well as evaluating study quality were completed independently by two investigators (W.A. and S.X.D.). Any discrepancy was solved by consultation with a third investigator (Y.B.).

We included all studies which reported serum or plasma adiponectin concentrations in CRC or adenoma (confirmed by colonoscopy or hispathological assay). Nonhuman studies, nonoriginal studies, genetic variation studies about adiponectin, and studies with overlapped population were excluded (Fig. 1).

Data extraction

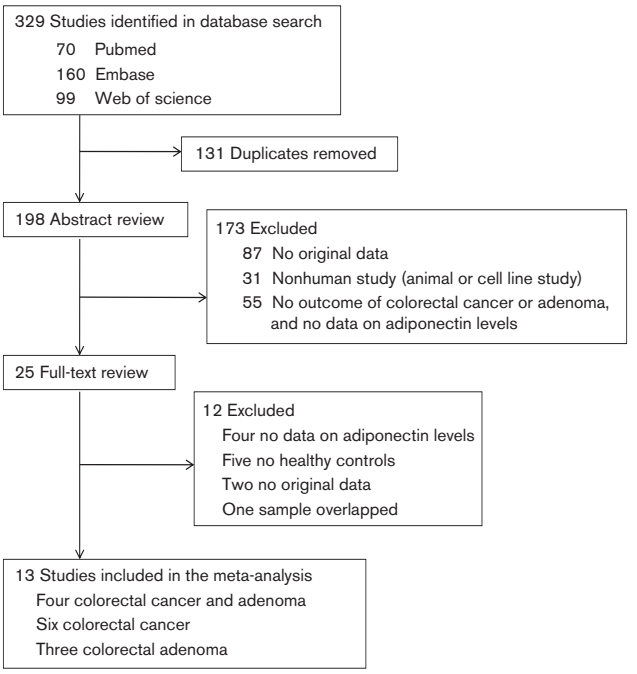
Two reviewers (W.A. and J.G.) independently extracted information and data from each study using standardized data abstraction forms. To settle differences, a third reviewer (Q.W.B.) was consulted. For each included article, we extracted information on the title, the authors, the publication year, the study location, the study design, the number of cases and controls, the male percentage, the type of blood sample, the methods of adiponectin detection, the source of reagent, the adiponectin levels [means and standard deviation (SD) or 95% confidence interval (CI) of means or median and interquartile range], the age, and the means of BMI estimation. To retrieve the missing data, we also contacted the authors of primary studies.

Statistical analysis

Adiponectin levels in each study were extracted as mean ± SD. Three studies did not provide the relevant data, although communication with authors had taken place. Means and SD values in two articles (Guadagni *et al.*, 2009; Nakajima *et al.*, 2010) were estimated based on the median and interquartile range (Hozo *et al.*, 2005; Liu *et al.*, 2007); SD values of the third article were transformed from 95% CIs. Records of two of the studies (Stocks *et al.*, 2008; Yamaji *et al.*, 2010) were entered separately for men and women, because adiponectin level data were stratified according to sex in these studies. Four articles presented results on adiponectin levels in patients with CRC and colorectal adenoma, respectively (Erarslan *et al.*, 2009; Kumor *et al.*, 2009; Nakajima *et al.*, 2010; Otake *et al.*, 2010). Therefore, the meta-analysis was based on 13 articles, 19 data points; 11 data points were used for the meta-analysis of adiponectin levels and CRC and the remaining eight data points were used for the meta-analysis of adiponectin levels and colorectal adenoma.

Weighted mean differences (WMDs) and corresponding 95% CIs were calculated from the raw data of the selected studies by using a random-effects model (DerSimonian and Laird, 1986). To investigate the sources of heterogeneity in these studies, we carried out heterogeneity tests, sensitivity analysis, and meta-regression analysis. For heterogeneity tests, we used Q and I^2 statistics to examine statistical heterogeneity among studies. For Q statistics, a P value of less than 0.1 was considered to be statistically significant. I^2 was interpreted as the percentage of total variation across studies due to heterogeneity. An I^2 value of greater than

Fig. 1



Flow diagram of the study selection process.

50% was considered to have significant heterogeneity and an I^2 value of less than 25% was considered to have no significant heterogeneity (Higgins *et al.*, 2003). Stratified analysis was conducted according to study location (Western vs. Asian population), study design (nested case–control vs. case–control study), sample size [continuous and two categories (≥ 100 vs. < 100 cases of CRC or adenoma)], type of blood sample (plasma vs. serum), assay methods of adiponectin levels (enzyme-linked immunosorbent assay vs. radioimmunoassay), mean age at baseline [continuous and two categories (≥ 60 vs. < 60 years)], matched for age (yes vs. no or not mentioned), mean BMI [continuous and two categories (≥ 25 vs. $< 25\,kg/m^2$)], and matched for BMI (yes vs. no or not mentioned). As all studies were case–control studies based on enzyme-linked immunosorbent assay, these two variables were not stratified for colorectal adenoma studies. We also carried out sensitivity analysis to estimate the influence of each individual study on the summary results by repeating the random-effects meta-analysis after omitting one study at a time. Given the insufficient data points in colorectal adenoma studies, restricted maximum likelihood-based random-effects metaregression analysis was only carried out in the CRC group to assess the above potential heterogeneous factors. Univariate meta-regression analyses were first carried out, after which the variables that were significant at the 0.1 level were included in the multivariable model. Publication bias was evaluated by using Egger's regression test, Begg's adjusted rank correlation test, and funnel plot (Begg and Mazumdar, 1994; Egger *et al.*, 1997). A two-sided P value less than 0.05 was considered statistically significant. All statistical analyses were carried out with Stata Statistical Software, version 10.0 (STATA, College Station, Texas, USA).

Results

Colorectal cancer

Ten articles (Wei *et al.*, 2005; Stocks *et al.*, 2008; Erarslan *et al.*, 2009; Guadagni *et al.*, 2009; Kumor *et al.*, 2009; Catalan *et al.*, 2011; Gonullu *et al.*, 2010; Kemik *et al.*, 2010; Nakajima *et al.*, 2010; Otake *et al.*, 2010) evaluating adiponectin levels in patients with CRC and healthy controls were identified in this meta-analysis; two of them (Wei *et al.*, 2005; Stocks *et al.*, 2008) were nested case–control studies (including 470 patients with CRC and 906 healthy controls), and eight were case–control studies (including 488 patients with CRC and 339 healthy controls). Seven studies were conducted in Europe, two in Japan, and one in the USA (Table 1).

The summary WMD of adiponectin concentration in patients with CRC was 1.51 unit (95% CI: -2.42 to -0.59) lower than that in healthy controls, with significant statistical heterogeneity ($I^2 = 84.5\%$, $P < 0.001$; Fig. 2a). In stratified analysis, the summary WMD of adiponectin levels comparing patients with CRC with healthy controls did not differ substantially according to study locations, types of blood sample, methods of adiponectin assay, age, BMI, mean age, and mean BMI of the study population (Table 2). Stratified analysis according to study design or sample size was also carried out; however, these associations were significantly different in each stratum. Summary WMD of adiponectin levels was significant in case–control studies [WMD, -2.40 (95% CI: -3.47 to -1.32), test for heterogeneity $I^2 = 60.8\%$, $P = 0.013$], but not in the nested case–control studies [WMD, -0.04 (95% CI: -0.70 to 0.62), test for heterogeneity $I^2 = 59.1\%$, $P = 0.087$]. Similarly, summary WMD of adiponectin levels was significant in studies with sample size of less than 100 [WMD, -3.07 (95% CI: -4.52 to -1.62), test for heterogeneity $I^2 = 51.9\%$, $P = 0.065$], but not in studies with sample size of more than 100 [WMD, -0.48 (95% CI: -1.49 to 0.54), test for heterogeneity $I^2 = 88.8\%$, $P < 0.001$].

Furthermore, we conducted meta-regression analyses to investigate the impact of the above study characteristics on the study estimates of WMD. The natural logarithm of WMD was the dependent variable, and study design, location, and confounding factors including BMI were entered as explanatory factors. In univariate meta-regression analysis, both study design ($P = 0.022$) and sample size ($P = 0.018$) were found to be significant factors. The between-study variance was reduced from 2.616 to 0.878 based on the restricted maximum likelihood estimate, the heterogeneity was explained by study design, and sample size was 66.44%. We also conducted a sensitivity analysis by omitting one study at a time and calculating the pooled WMDs for the remaining studies, and found that there were no changes in the direction of effect when any one study was excluded (Fig. 3a).

There was no funnel plot asymmetry detected in these studies evaluating adiponectin levels in patients with CRC and healthy controls. P values for Begg's adjusted rank correlation test ($P = 0.119$) and Egger's regression asymmetry test ($P = 0.147$) were more than 0.05, suggesting a low probability of publication bias.

Colorectal adenoma

Seven case–control studies (Otake *et al.*, 2005, 2010; Fukumoto *et al.*, 2008; Erarslan *et al.*, 2009; Kumor *et al.*, 2009; Nakajima *et al.*, 2010; Yamaji *et al.*, 2010), including 1674 cases of colorectal adenoma and 1609 healthy controls, presented results of adiponectin levels in patients with colorectal adenoma and healthy controls. Five of them were carried out in Japan and two in Europe (Table 1). Summary WMD of adiponectin levels in patients with colorectal adenoma was 1.29 unit (95% CI: -2.01 to -0.58) lower than that in healthy controls, with statistically significant heterogeneity ($I^2 = 87.1\%$, $P < 0.001$, random-effects model; Fig. 2b). We then performed stratified analysis according to the studies' various characteristics, including sample size, study location, type of blood sample, age, BMI,

Table 1 Characteristics of the studies of colorectal tumor and adiponectin in meta-analysis

Disease	References	Country	Study design	Blood sample	Assay method	Assay resource	Case/control, no.	Mean ± SD (μg/ml) case/control
Colorectal cancer	Stocks *et al.* (2008)	Sweden	Nested case–control	Plasma	ELISA	R & D Systems	Men 113/210	7.85 ± 4.15/7.18 ± 3.18
							Women178/340	11.90 ± 5.70/12.06 ± 5.37
	Wei *et al.* (2005)	USA	Nested case–control	Plasma	RIA	Linco Research	179/356	7.40 ± 2.10/7.80 ± 1.90
	Nakajima *et al.* (2010)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	115/115	8.90 (6.6–13)/8.9(5.7–12.9)[a]
	Otake *et al.* (2010)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	51/26	8.40 ± 5.10/12.00 ± 5.00
	Kemik *et al.* (2010)	Turkey	Case–control	Serum	RIA	Linco Research	126/38	4.30 ± 2.50/6.50 ± 1.40
	Gonullu *et al.* (2010)	Turkey	Case–control	Serum	ELISA	BioSource	36/37	5.50 ± 5.20/6.20 ± 3.00
	Guadagni *et al.* (2009)	Italy	Case–control	Serum	ELISA	BioVendor Laboratory Medicine	90/30	8.10 (5.7–9.3)/13.10(12.2–15.6)[a]
	Kumor *et al.* (2009)	Poland	Case–control	Serum	ELISA	R & D Systems	36/25	12.00 ± 4.90/17.80 ± 7.80
	Erarslan *et al.* (2009)	Turkey	Case–control	Plasma	ELISA	RayBio	23/50	7.10 ± 3.40/9.20 ± 3.80
	Catalan *et al.* (2011)	Spain	Case–control	Plasma	ELISA	R & D Systems	11/18	4.07 ± 1.76/8.09 ± 3.82
Colorectal adenoma	Nakajima *et al.* (2010)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	72/72	7.50 (5.4–10.3)/8.80(6.3–13.6)[a]
	Otake *et al.* (2010)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	47/26	8.20 ± 4.80/12.00 ± 5.00
	Fukumoto *et al.* (2008)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	656/648	5.42 (5.24–5.61)/5.63(5.43–5.84)[b]
	Otake *et al.* (2005)	Japan	Case–control	Plasma	ELISA	Otsuka Pharmaceutical	51/52	7.00 ± 2.60/10.60 ± 2.50
	Yamaji *et al.* (2010)	Japan	Case–control	Plasma	ELISA	Sekisui Medical	Men 524/481	4.42 ± 2.09/4.88 ± 2.45
							Women 256/255	7.29 ± 3.42/7.50 ± 3.30
	Kumor *et al.* (2009)	Poland	Case–control	Serum	ELISA	R & D Systems	37/25	15.40 ± 7.60/17.80 ± 7.80
	Erarslan *et al.* (2009)	Turkey	Case–control	Plasma	ELISA	RayBio	31/50	7.40 ± 3.75/9.20 ± 3.80

ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; SD, standard deviation.
[a]Median (interquartile range).
[b]Mean (95% confidence interval).

mean age, and mean BMI of the study population, and found that summary WMD of adiponectin levels comparing cases of colorectal adenoma with healthy controls tended to be somewhat stronger for studies with sample size of less than 100 [WMD, −2.73 (95% CI: −3.80 to −1.67), $I^2 = 36.9\%$] than those studies with sample size more than 100 [WMD, −0.32 (95% CI: −0.51 to −0.13), $I^2 = 0\%$]. There was no statistically significant heterogeneity according to study location, type of blood sample, mean age, and mean BMI of the study population (Table 2). We also conducted a sensitivity analysis by omitting one study at a time; when the study by Otake *et al.* (2005) was excluded, the pooled WMD was greatly changed, but the direction of effect was not changed (Fig. 3b). The funnel plot was slightly asymmetrical, however neither Egger's test ($P = 0.072$) nor Begg's test ($P = 0.174$) showed statistically significant publication bias.

Discussion

The results of this meta-analysis suggest that adiponectin levels are significantly lower in patients with CRC or adenoma compared with healthy controls. The decreased levels of adiponectin are found to be consistent for both men and women with CRC or adenoma, for various assay methods and for various mean BMI.

Findings from this study also indicate that adiponectin levels may be inversely associated with risk of CRC and adenoma. There are several mechanisms proposed to explain these observations. In-vitro studies conducted by Sugiyama *et al.* (2009) and Fenton *et al.* (2008) indicated that adiponectin could inhibit CRC cell or preneoplastic colon epithelial cell growth and proliferation through activation of the adenosine monophosphate-activated protein kinase pathway and subsequent inhibition of the mammalian target of rapamycin pathway (Fujisawa *et al.*, 2008; Sugiyama *et al.*, 2009). Animal studies showed that adiponectin knockout mice had increased numbers of colorectal tumors compared with wild type (Fujisawa *et al.*, 2008; Nishihara *et al.*, 2008; Mutoh *et al.*, 2011). Furthermore, some studies (Kaklamani *et al.*, 2008; Carvajal-Carmona *et al.*, 2009; Pechlivanis *et al.*, 2009) have related adiponectin gene variants with

Table 2 Stratified meta-analysis of adiponectin levels and colorectal tumor

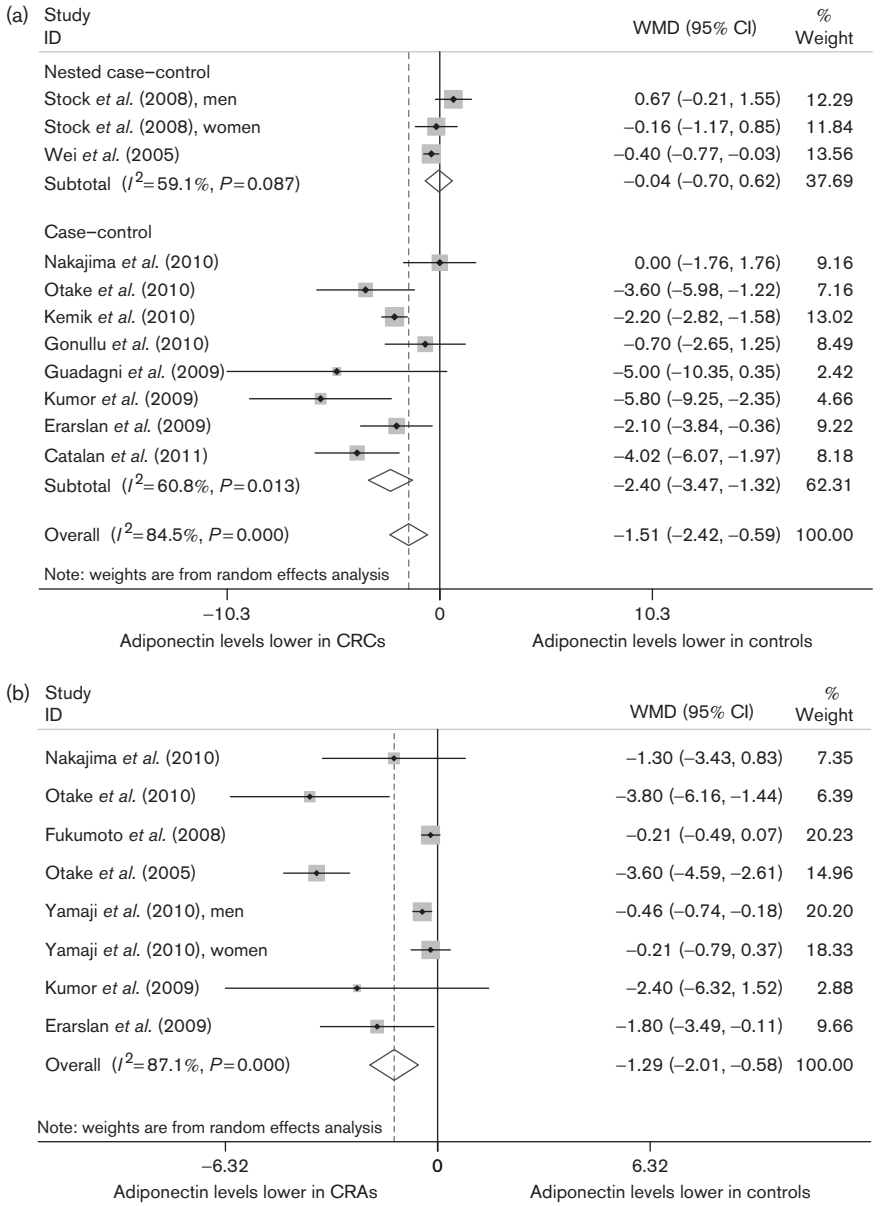
			Heterogeneity test		
Stratification group	Data points, no.	WMD (95% CI)	*Q*	*P*	I^2 (%)
Colorectal cancer	11	−1.51 (−2.42 to −0.59)	64.47	<0.001	84.5
Study location					
Western	9	−1.49 (−2.49 to −0.49)	58.34	<0.001	86.3
Asian (Japan)	2	−1.71 (−5.23 to 1.82)	5.69	0.017	82.4
Study design					
Nested case–control	3	−0.04 (−0.70 to 0.62)	4.89	0.087	59.1
Case–control	8	−2.40 (−3.47 to −1.32)	17.88	0.013	60.8
Sample size					
<100 CRC cases	6	−3.07 (−4.52 to −1.62)	10.40	0.065	51.9
≥ 100 CRC cases	5	−0.48 (−1.49 to 0.54)	35.63	<0.001	88.8
Blood sample					
Plasma	7	−1.00 (−1.95 to −0.06)	28.71	<0.001	79.1
Serum	4	−2.60 (−4.36 to −0.84)	7.50	0.058	60.0
Assay method					
ELISA	9	−1.77 (−3.10 to −0.45)	40.18	<0.001	80.1
RIA	2	−1.28 (−3.05 to 0.48)	23.83	<0.001	95.8
Mean age, years					
<60	6	−1.33 (−2.72 to 0.06)	39.39	<0.001	87.3
≥ 60	5	−2.08 (−3.91 to −0.24)	21.01	<0.001	81.0
Matched for age					
Yes	10	−1.25 (−2.16 to −0.35)	54.83	<0.001	83.6
No or not mention	1	−4.02 (−6.07 to −1.97)	0	–	–
Mean BMI[a], kg/m^2					
<25	4	−2.08 (−3.66 to −0.50)	8.23	0.042	63.5
≥ 25	7	−1.17 (−2.19 to −0.15)	31.03	<0.001	80.7
Matched for BMI					
Yes	8	−1.00 (−1.98 to −0.02)	30.45	<0.001	77.0
No or not mentioned	3	−2.27 (−2.84 to −1.70)	1.29	0.525	0.0
Colorectal adenoma	8	−1.29 (−2.01 to −0.58)	54.47	<0.001	87.1
Study location					
Western	2	−1.89 (−3.44 to −0.34)	0.08	0.783	0.0
Asian (Japan)	6	−1.20 (−1.97 to −0.44)	51.15	<0.001	90.2
Sample size					
<100 CRA cases	5	−2.73 (−3.80 to −1.67)	6.34	0.175	36.9
≥ 100 CRA cases	3	−0.32 (−0.51 to −0.13)	1.69	0.430	0.0
Blood sample					
Plasma	7	−1.26 (−1.99 to −0.53)	53.54	<0.001	88.8
Serum	1	−2.40 (−6.32 to 1.52)	0	–	–
Mean age, year					
<60	3	−1.26 (−2.76 to 0.24)	42.73	<0.001	95.3
≥ 60	5	−1.61 (−2.89 to −0.33)	11.09	0.026	63.9
Matched for age					
Yes	7	−1.68 (−2.81 to −0.55)	54.43	<0.001	89.0
No or not mentioned	1	−0.46 (−0.74 to −.0.18)	0	–	–
Mean BMI[a], kg/m^2					
<25	6	−1.20 (−1.97 to −0.44)	51.15	<0.001	90.2
≥ 25	2	−1.89 (−3.44 to −0.34)	0.08	0.783	0.0
Matched for BMI					
Yes	5	−2.19 (−4.18 to −0.20)	38.89	<0.001	89.7
No or not mentioned	3	−0.39 (−0.75 to −0.04)	4.40	0.111	54.6

CI, confidence interval; CRA, colorectal adenoma; CRC, colorectal cancer; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; WMD, weighted mean difference.
[a]Calculated as weight in kilograms divided by height in meters squared.

risk of CRC, and found that single nucleotide polymorphism rs266729 on the adiponectin gene was associated with a decreased CRC risk (Kaklamani *et al.*, 2008; Pechlivanis *et al.*, 2009). The evidence mentioned above suggests that adiponectin may be involved in the pathogenesis of CRC.

However, several potential limitations should be considered in the interpretation of the findings. First, there was significant heterogeneity observed across studies, which would reduce the reliability of these results. Although we investigated sources of heterogeneity by conducting stratified analysis and metaregression analysis, only part of the inconsistency (66.44%) was explained by study design and sample size. The results suggested that in studies with smaller samples or retrospective design, adiponectin levels were found to be significantly lower in patients with CRC than healthy controls. In contrast, in studies with lager sample size or prospective design, no difference in adiponectin levels was observed. Similarly, difference in adiponectin levels between patients with colorectal adenoma and controls was only found in studies with smaller sample size, but not in studies with larger sample size. Therefore, it may be inferred that design and

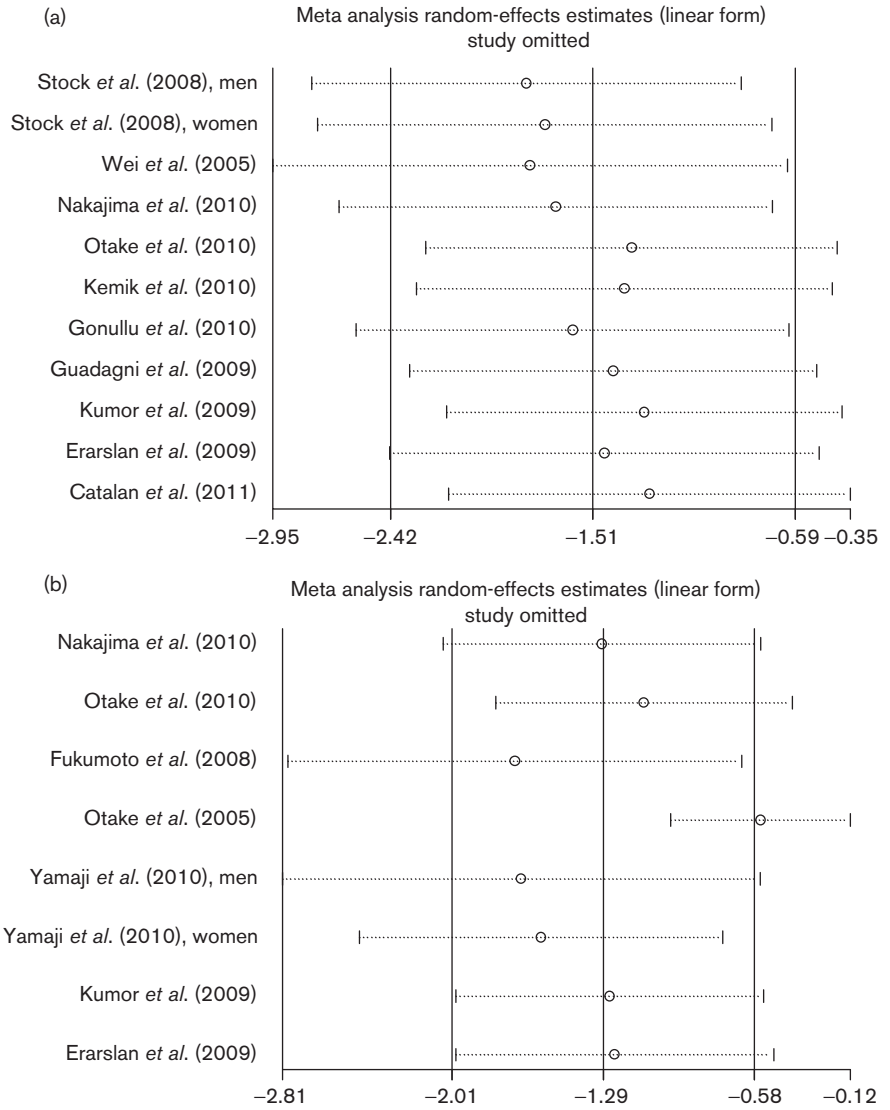
Fig. 2



(a) Weighted mean adiponectin levels in colorectal cancers (CRCs) and controls and pooled estimate. (b) Weighted mean adiponectin levels in colorectal adenomas (CRAs) and controls and pooled estimate.

sample size might be important factors, which induced discrepancy in the results of each study. In addition, it may also be inferred that available evidence in this meta-analysis failed to establish a cause-and-effect relationship between adiponectin and colorectal tumor development. Second, accumulating evidence suggests that adiponectin levels are closely related with obesity and type 2 diabetes (T2DM; Trujillo and Scherer, 2005; Li *et al.*, 2009; Nayak *et al.*, 2010; Hivert *et al.*, 2011), which are two important risk factors for the development of colorectal tumor (Larsson *et al.*, 2005; Larsson and Wolk, 2007). Therefore, both obesity and T2DM could be important confounders. Subgroup analyses by BMI stratification showed no difference between subgroups, which suggested that the association between adiponectin levels and colorectal tumor may be independent of BMI. However, it was a great pity that the influence of visceral adiposity and IR could not be checked, as data on waist circumference, waist-to-hip ratio, or visceral fat accumulation, and IR index (Homeostasis Model of Assessment-IR), or number of patients with T2DM were not available in the majority of studies. Third, although the results of meta-analysis in the remaining colorectal adenoma studies were still statistically significant after omitting the study by Otake

Fig. 3



(a) Influence of removing studies one by one on adjusted effect estimates for colorectal cancer. (b) Influence of removing studies one by one on adjusted effect estimates for colorectal adenoma. Circles are effect estimates and horizontal dotted lines are 95% confidence intervals for meta-analysis of the remaining studies; the vertical line in the center is the pooled effect estimate for all studies.

et al. (2005), the study exerted a strong influence on the meta-analysis estimate of effect. Given that adiponectin concentration was negatively correlated with abdominal obesity (Hanley *et al.*, 2007), association between adiponectin levels and risk of colorectal adenoma may be exaggerated in the study conducted by Otake *et al.* (2005). This could be because the visceral fat accumulation in the patients was significantly larger than those in the controls in this study. Finally, as small studies with null results may not be published, the possibility of publication bias is a concern. In addition, the sensitivity of both Egger's test and Begg's test is generally low in the meta-analyses based on fewer than 20 studies (Jonathan and Sterne, 2001). Therefore, it is difficult to evaluate the influence of publication bias accurately.

In summary, this study indicates that adiponectin levels in patients with CRC or colorectal adenoma are significantly lower than those in healthy controls, which suggests that adiponectin may be involved in the development of colorectal tumor. However, these findings were based on studies with retrospective design or studies with small sample sizes. Further studies, both epidemiological and experimental, are warranted to clarify the association between adiponectin and the development of CRC or colorectal adenoma.

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Conflicts of interest

There are no conflicts of interest.

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