

Association between obesity-related adipokines and colorectal cancer: A case-control study and meta-analysis

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Abstract

AIM: To examine the association between obesity-related adipokines (adiponectin, leptin, resistin, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α)) and colorectal cancer (CRC) risk.

METHODS: Serum levels of adipokines were measured in 100 CRC patients and age- and sex-matched controls for the data analysis. Unconditional logistic regression models were used for estimating ORs and 95% CIs related to each adipokine. For the meta-analysis, studies published before July 2013 available on Medline/PubMed and EMBASE were retrieved. The analysis included a total of 17 relevant studies (including the present case-control study): nine studies on adiponectin and eight on leptin. The effect sizes of

ORs and 95% CIs were estimated using RevMan 5.1. Heterogeneity was evaluated using Cochran's Q -test and I^2 statistics.

RESULTS: Among the five adipokines, only resistin levels were significantly higher in cases than in controls ($P < 0.001$). The case-control study results showed no association between adiponectin and CRC and a negative association between leptin and CRC. However, the results of the meta-analysis showed a significant inverse association between adiponectin and CRC (OR = 0.91, 95%CI: 0.83-1.00, $P = 0.04$) and no association between CRC and leptin. After stratification by study design, an inverse association between adiponectin and CRC was observed in prospective studies only (OR = 0.90, 95%CI: 0.82-0.99, $P = 0.03$), whereas the association between leptin and CRC was inconsistent (prospective studies: OR = 1.14, 95%CI: 1.02-1.27, $P = 0.02$ and retrospective studies: OR = 0.47, 95%CI: 0.29-0.74, $P = 0.001$). The associations of resistin and TNF- α with CRC risk were positive, but no association was observed for IL-6.

CONCLUSION: Our results suggest a negative association of leptin, positive associations of resistin and TNF- α , and null associations of adiponectin and IL-6 with CRC. However, further studies with larger number of prospective approaches are needed.

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Key words: Obesity; Colorectal cancer; Cancer risk; Adipokines; Obesity-related adipokines

Core tip: Evidence from the previous studies indicates that there is an association of obesity-related adipokines and pro-inflammatory cytokines with colorectal cancer risk, but the results are inconsistent. In this study, a case-control study and meta-analysis were performed to investigate the possible association of adipokines (adiponectin, leptin, and resistin) and pro-

inflammatory cytokines (interleukin-6 and tumor necrosis factor- α) with colorectal cancer risk. Although we did not find any significant results, case-control study and meta-analysis results support a previous report and suggest that obesity-related adipokines could be risk factors for colorectal cancer; however, further studies with larger number of prospective approaches are needed.

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INTRODUCTION

Colorectal cancer (CRC) is a major public health concern, as it is one of the leading causes of cancer deaths worldwide. Although the highest incidence rate of CRC is observed in developed countries, including Australia, New Zealand, Canada, and the United States, as well as countries in North Western Europe, its incidence rate has been rapidly increasing in developing countries in the past few decades^[1]. In particular, East Asian countries such as China, Japan, South Korea, and Singapore have experienced a two- to four-fold increase in CRC incidence in recent decades^[2,3]. In South Korea, the incidence of CRC increased from 20.4 per 100000 to 35.9 per 100000 from 1999 to 2010, with a 5.9% annual percentage change in age-standardized incidence rates^[4].

Obesity, particularly central obesity, has been consistently identified as the most recognized risk factor for CRC^[5,6]. Furthermore, obesity is significantly associated with a 7%-60% increase in CRC risk compared to normal weight individuals [body mass index (BMI) < 25 kg/m²]^[7-9]. However, the etiologic mechanisms underlying this association are not well understood. It is hypothesized that insulin and adipokines are key regulators for the potential link between obesity and CRC. First, obesity may lead to insulin resistance and hyperinsulinemia, which consequently reduces IGFBP-1 levels while elevating levels of IGF-1; it also increases cell proliferation and inhibits apoptosis^[10-13]. Second, obesity alters the level of adipose tissue-derived adipokines, including adiponectin, leptin, and resistin, and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). Increased levels of these adipokines can cause initiation, progression, and metastasis of tumors, with the exception of adiponectin, which has anti-inflammatory and insulin-sensitizing properties^[14,15]. Experimental studies have demonstrated that pro-inflammatory cytokines such as IL-6 and TNF- α may promote tumor growth by acting as mitogens for normal and neoplastic colon cells^[15] and by inducing leptin and resistin production^[16,17], which stimulates survival and

growth of colon cancer cells directly or indirectly by increasing IL-6 and TNF- α ^[16,18]. In contrast, adiponectin has anti-carcinogenic effects, including inhibition of cell growth and induction of apoptosis^[19].

Due to the bioactivities of adipokines, several prospective and retrospective epidemiologic studies have examined the association between circulating levels of adipokines related to CRC risk; however, the results have been inconclusive. Although few prospective studies^[20-22] have shown an inverse association between low adiponectin and CRC, other studies have found conflicting results^[23,24]. It has been suggested that CRC risk increases with increased levels of leptin^[21,25] and resistin^[23,26], yet this increase is unsupported by other studies^[27,28]. Similarly, three prospective studies^[21,29,30] on IL-6 and TNF- α , have reported inconsistent results. Although there are some discrepancies among studies, it could be speculated that circulating levels of adipokines are possible candidate biomarkers for CRC risk. Thus, early identification of such risk factors can be useful for screening purposes and may help prevent and control CRC.

The aim of the present case-control study is to assess the association of five adipocytokines (adiponectin, leptin, resistin, TNF- α , and IL-6) with CRC risk and to perform a meta-analysis using results from different countries to describe the effect of adiponectin and leptin on CRC risk.

MATERIALS AND METHODS

Patients and samples

The specimens used for this study were collected from the Keimyung Human Bio-Resource Bank, a member of the National Bio-bank of South Korea, which is supported by the Ministry of Health and Welfare, South Korea and Kangwon National University Bio-bank. All of the samples were therefore derived from the National Bio-bank of South Korea and subject to informed consent under institutional review board-approved protocols. After the study protocols were approved, the study was conducted at Keimyung and Kangwon National University Hospital from 2009-2011. Patients from Keimyung University Hospital who had been newly and pathologically diagnosed with colorectal cancer by biopsy using colonoscopy were identified as colorectal cancer patients. Similarly, age- and sex-matched controls from Kangwon National University Hospital were identified among individuals who received negative diagnoses for colorectal cancer by serological blood test. The cases and controls were then subsequently matched for each 100:100 as selected for the study. The age strata for the analysis were ≤ 60 , 61-70, and $71 \geq$ in selected cases and controls. The study was approved by the National Bio-bank of South Korea, and all participants provided informed consent under institutional review board-approved protocols (IRB No. 2010-10-008).

Measurement of serum adipokines

Blood samples were collected from the patients and age/

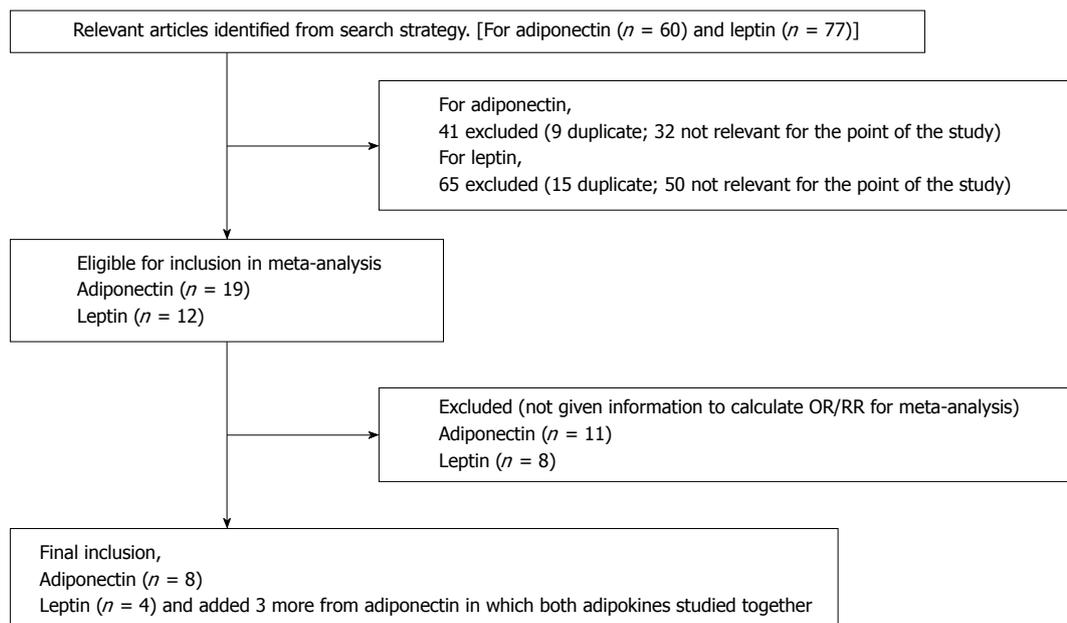


Figure 1 Result of literature search for meta-analysis.

sex-matched individuals. Serum separated from the blood samples was stored at -20°C for further analysis. Serum levels of adiponectin were determined by enzyme-linked immunosorbent assay (ELISA) (AdipoMark, South Korea) per the manufacturer's instructions, with a sensitivity of 1.39 ng/mL and an intra-assay coefficient of variation of 4.1%-5.9%. ELISA (Enzo Life Science, United States) was used to measure leptin with a sensitivity of 23.4 pg/mL and an intra-assay coefficient of variation of 4.4%-13.4%. Resistin levels were measured using a resistin (human) ELISA kit (Adipogen, Switzerland) with a sensitivity of 100 pg/mL and an intra-assay coefficient of variation 2.86%-3.73%. Enzyme Immunoassay (Enzo Life Science, United States) was used to measure the serum levels of IL-6 and TNF- α . The sensitivities of IL-6 and TNF- α were 6.01 pg/mL and 8.43 pg/mL, respectively, and the intra-assay coefficients of variations were 3.8%-6.4% and 4.5%-3.6%, respectively.

Meta-analysis

To collect the studies for the meta-analysis, we searched the PubMed/Medline and EMBASE databases using the following keywords for published papers: "plasma and/or serum", "adiponectin and/or leptin" and "colorectal cancer". The articles included in this meta-analysis were all eligible prospective and retrospective studies on CRC published before July 2013. The studies that included OR or RR but did not use original data to calculate these values were excluded. The study selection strategy is presented in Figure 1. We included a total of eight studies on adiponectin and CRC and seven studies on leptin and CRC. The number of the cases and controls varied widely among studies. Therefore, for the meta-analysis we used median variables; if the study group was categorized by quartile, we rearranged the number by median,

as q^1 and q^2 (reference group) *vs* q^3 and q^4 (compared group). Likewise, if the study group was categorized by quintile, we rearranged the number as 1st, 2nd and 3rd quintile (reference group) *vs* 4th and 5th quintile (compared group). Next, the pooled odds ratios from the selected studies were calculated to evaluate the strength of the association of adiponectin and leptin with CRC, which is presented as the result of the current meta-analysis. Cochran's χ^2 test^[31] and the inconsistency index (I^2)^[32] were used to evaluate heterogeneity across the studies. To calculate the summary OR, a fixed-effect model was used if $P > 0.10$ or $P \leq 0.10$, but $I^2 \leq 50\%$ indicates lack of heterogeneity^[33]. Otherwise, a random-effects model was used when $P \leq 0.10$ and $I^2 > 50\%$, which indicates significant heterogeneity^[34]. To determine the statistical significance of pooled the odds ratios, Z-tests were performed and considered significant when $P < 0.05$. Additionally, we performed a stratification analysis of the study designs (prospective *vs* retrospective) to explore the association of adiponectin and leptin with CRC. Finally, potential publication bias was assessed using Begg's funnel plot and Egger's regression test^[35,36]. $P < 0.05$ was chosen as the level of statistical significance for publication bias.

Statistical analysis

The baseline characteristics of colorectal cancer cases and controls were compared using a *t* test for continuous variables and a χ^2 test for categorical variables. The association between adipokines and CRC was examined *via* unconditional logistic regression model expressed as univariate odds ratios (OR1s) and multivariate odds ratios (OR2s) with 95% CIs after adjusting for age, sex and covariates, including the selected adipokines. To calculate odds ratios, a median value was used for resistin due to the skewed blood level distribution, and tertiles that

Table 1 Serum adipokine levels in patients with colorectal cancer and healthy controls *n* (%)

	Total	Case	Control	<i>P</i> value
Age ¹	66.5 ± 10.0	66.1 ± 10.0	66.9 ± 10.0	0.67
≤ 60	39 (19.5)	20 (20.0)	19 (19.0)	
61-70	87 (43.5)	46 (46.0)	41 (41.0)	
≥ 71	74 (37.0)	34 (34.0)	40 (40.0)	
Sex				1.00
Male	120 (60.0)	60 (60.0)	60 (60.0)	
Female	80 (40.0)	40 (40.0)	40 (40.0)	
Serum levels				
Adiponectin (µg/mL) ¹	6.0 ± 4.9	5.7 ± 4.4	6.2 ± 5.3	0.47
Leptin (ng/mL) ¹	7.8 ± 8.9	6.8 ± 9.3	8.8 ± 8.5	0.12
Resistin (ng/mL) ¹	3.9 ± 2.3	4.9 ± 2.3	2.8 ± 1.7	<0.0001
IL-6 (pg/mL) ¹	21.0 ± 103.6	11.3 ± 11.8	30.8 ± 145.8	0.19
TNFα (pg/mL)	6.0 ± 13.2	6.4 ± 12.5	5.7 ± 13.9	0.68

¹Value is mean ± SD. *P* value for the comparison of cases and controls by *t* test or χ^2 test, as appropriate. TNF: Tumor necrosis factor; IL: Interleukin.

were used for rest of the adipokines. Furthermore, we performed the analysis assuming all selected adipokines as continuous variables and as categorical variables in tertiles to assess the cumulative risk effects of adipokines on CRC. Each adipokines was coded as 1, 2, or 3 for adiponectin and 0, 1, or 2 for other adipokines and was calculated using the sum of the numbers. Statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute) for case-control study analysis and RevMan software (version 5.1, Cochrane Collaboration) and STATA Software (version 10.0) for the meta-analysis.

RESULTS

Table 1 shows the baseline characteristics of case and control participants. Of the total participants, 60% were male and 40% were female. The corresponding mean values for serum adipokines were 6.0 ± 4.9 µg/mL, 7.8 ± 8.9 ng/mL, 3.9 ± 2.3 ng/mL, 21.0 ± 103.6 pg/mL, and 6.0 ± 13.2 pg/mL for adiponectin, leptin, resistin, IL-6, and TNF-α, respectively. The mean levels of all examined adipokines were very similar in cases and controls, except for resistin, which was significantly higher in cases (4.9 ± 2.3 ng/mL) than in controls (2.8 ± 1.7 ng/mL) (*P* ≤ 0.0001) (Table 1).

The results of the univariate and multivariate logistic regression analyses for the association between each adipokines and CRC are shown in Table 2. Serum levels of resistin and TNF-α were significantly positively associated with the risk of CRC; moreover, the association was increased significantly for both adipokines after adjusting covariates (OR = 6.08, 95%CI: 3.23-11.44 and OR = 41.16, 95%CI: 12.62-134.23; *P*-trend ≤ 0.01, respectively). An inverse association was observed between leptin and CRC, and the association remained consistent even after adjusting covariates (OR = 0.31, 95%CI: 0.14-0.73; *P*-trend

= 0.01). In contrast, there was no association with adiponectin and IL-6 and CRC risk (Table 2). Additionally, we evaluated the association among the combined score of the adipokines and risk of CRC; however we found no combined effect using the weighted score of each adipokines (data not shown).

The results of the meta-analysis using prospective and retrospective studies including the present study showed adiponectin to be negatively associated with CRC risk (OR = 0.91, 95%CI: 0.83-1.00, *P* = 0.04). After stratification, the association remained significant, predominantly in prospective studies (OR = 0.90, 95%CI: 0.82-0.99, *P* = 0.03) (Figure 2). For leptin, no significant association with CRC was observed; however, in an analysis stratified by study design (prospective *vs* retrospective), a positive association was observed in prospective studies (OR = 1.14, 95%CI: 1.02-1.27, *P* = 0.02), while a negative association was observed in retrospective studies (OR = 0.47, 95%CI: 0.29-0.74, *P* = 0.001) (Figure 3). Publication bias of the meta-analysis regarding the association of adiponectin and leptin with CRC was also examined, but the evaluation of publication bias did not yield statistically significant results (data not shown).

DISCUSSION

In our case-control study using a Korean population, adiponectin was not associated with CRC risk; however, the overall results of meta-analysis suggest a significant inverse association of adiponectin with CRC risk, particularly in prospective studies. For leptin, we found a significant inverse association with CRC in our case-control study, although the meta-analysis showed no association. Furthermore, after stratification by study design, the association was found to be inconsistent; negative association was observed in the meta-analysis using retrospective studies, while a positive association was observed in the prospective studies. For the other selected adipokines, including resistin, IL-6 and TNF-α, we found a significant positive association of resistin and TNF-α with CRC risk, but no association of IL-6 with CRC risk.

It has been proposed that adiponectin may inhibit CRC cell growth and proliferation through several pathways, including the STAT3/ NF-κB, AMPK, and MAPK pathways, resulting in a protective effect on CRC risk^[37]. Several epidemiological studies have examined the association between low circulating adiponectin and increased risk of CRC^[28,38,39], but other studies have not supported this association^[23,24]. Thus far, among the several prospective studies that have been conducted^[20,21,24,40-42], two studies from an EPIC^[20] and WHI-OS^[21] have suggested that an inverse association between low adiponectin and CRC was attenuated and did not retain significance after adjusting for BMI and WC. Other studies^[40,41] have proposed that men with the highest concentrations of adiponectin had reduced risk for CRC compared to men with the lowest concentrations, even after adjusting for BMI. However, two studies^[24,42] could not confirm the

Table 2 Association between each obesity-related adipokine and colorectal cancer risk

	Case (n = 100)	Control (n = 100)	OR	OR1
Adiponectin (µg/mL)				
1 st tertile	31	35	Ref.	Ref.
2 nd tertile	39	28	1.57 (0.79-3.12)	1.76 (0.79-3.91)
3 rd tertile	30	37	0.92 (0.46-1.81)	0.80 (0.34-1.87)
<i>P-trend</i>			0.80	0.65
Leptin (ng/mL)				
1 st tertile	45	21	Ref.	Ref.
2 nd tertile	26	41	0.30 (0.15-0.60)	0.37 (0.17-0.83)
3 rd tertile	29	38	0.36 (0.18-0.72)	0.31 (0.14-0.73)
<i>P-trend</i>			0.05	0.01
Resistin (ng/mL)				
Low	30	70	Ref.	Ref.
High	70	30	5.44 (2.97-9.97)	6.08 (3.23-11.44)
<i>P-trend</i>			< 0.0001	< 0.0001
IL-6 (pg/mL)				
1 st tertile	43	25	Ref.	Ref.
2 nd tertile	26	42	0.36 (0.18-0.72)	0.46 (0.21-1.01)
3 rd tertile	31	33	0.55 (0.27-1.10)	0.55 (0.24-1.26)
<i>P-trend</i>			0.82	0.14
TNFα (pg/mL)				
1 st tertile	14	54	Ref.	Ref.
2 nd tertile	34	32	4.10 (1.92-8.77)	5.08 (1.84-13.10)
3 rd tertile	52	14	14.33 (6.23-32.95)	41.16 (12.62-134.23)
<i>P-trend</i>			< 0.01	< 0.01

OR: Age, sex matched odds ratio; OR1: Odds ratio after adjusting each obesity-related adipokines. IL: Interleukin; TNF: Tumor necrosis factor.

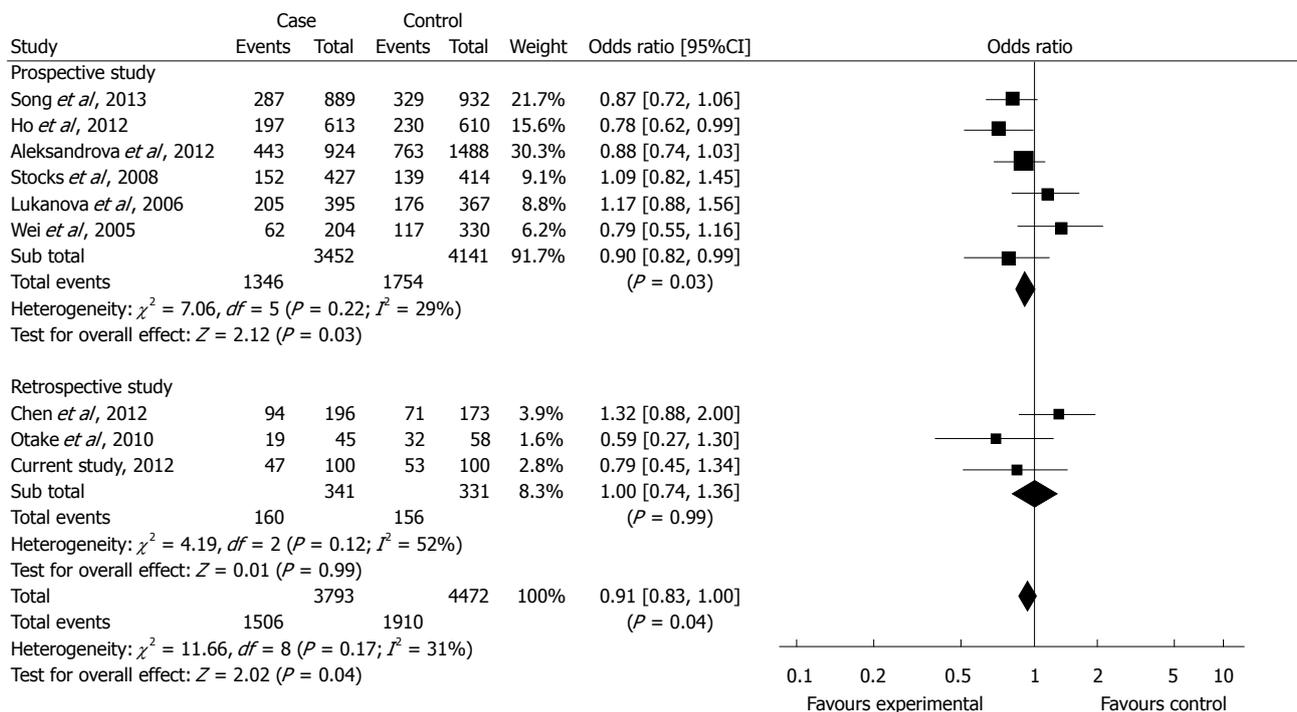


Figure 2 Meta-analysis for the association between adiponectin and colorectal cancer.

significant differences regarding the level of adiponectin among CRC patients and controls, and they also failed to describe the association. In retrospective studies, the results regarding an association between adiponectin and CRC are also inconsistent. Two case-control studies^[43,44] have consistently reported a significantly increased risk

of CRC in patients with decreased levels of adiponectin, predominantly for early cancer, with the risk persisting even after adjusting for BMI, WHR, or other lifestyle factors. In contrast, a study^[23] conducted in Japan did not find any association between adiponectin and CRC among BMI matched cases and controls. In the pres-

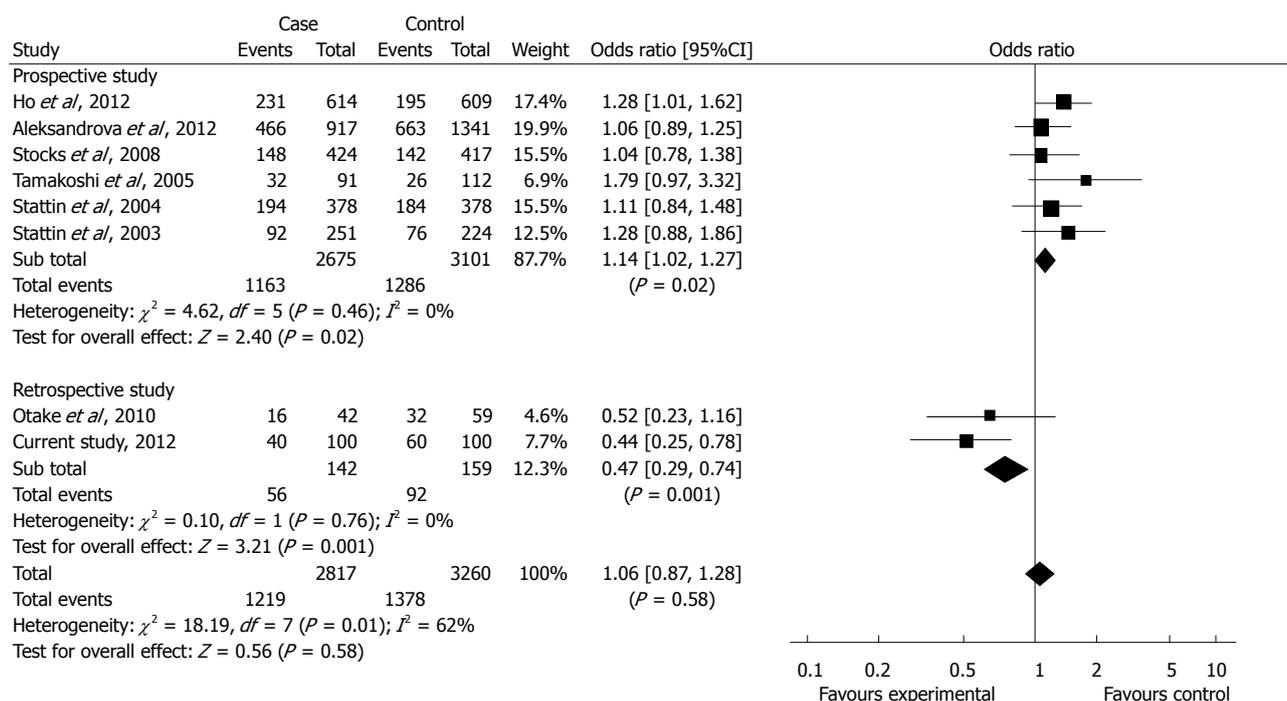


Figure 3 Meta-analysis for the association between leptin and colorectal cancer.

ent study, we were unable to find any differences in adiponectin level between cases and control and did not observe any association; however, our meta-analysis results showed an inverse association between adiponectin and CRC risk, which is consistent with another recently published meta-analysis^[45]. Furthermore, after stratifying by ethnicity, the inverse association between adiponectin and CRC was stronger among Asians compared to Caucasians (results not shown). The difference in ethnicity, however, must be interpreted with caution due to the lack of power based on the small number of studies among Asian populations compared to the number conducted in Caucasian populations. Therefore, further investigations that include other ethnic groups, including other Asians, are needed to confirm and expand these findings.

In contrast to adiponectin, leptin has tumorigenic bioactivity and regulates angiogenesis or apoptosis through several signaling pathways, including the PI3K/Akt pathway *via* up-regulation of IRS, JAK/STAT3 and the mitogenic pathway *via* ERK1/2 or JNK^[37]. The association between leptin levels and CRC risk remains controversial. In the present study, the finding of an inverse association between leptin and CRC is consistent with previously published case-control studies^[27,28,46]. The results from our meta-analysis indicated that elevated levels of leptin are not associated with CRC risk, which is consistent with another recent meta-analysis^[47]. However, while a negative association between leptin and CRC risk has been observed in retrospective studies after stratification by study design, the association has been positive in prospective studies. In contrast, most previous prospective studies^[21,25,48,49] reported a positive

association between elevated leptin levels and CRC risk after adjustment for BMI or WC, whereas one study^[49] reported that leptin is associated CRC risk independently of BMI. Additionally, the results from our meta-analysis among Asians and Caucasians, showed a significant positive association between leptin and CRC only among Caucasians. However, it is difficult to compare the differences between Asians and Caucasians due to the limited amount of available research. It was also found that circulating leptin levels were relatively higher in Caucasians than Asians^[50]. Overall, the inconsistencies in the literature may be due to variations in sample size, study design, or adjustment of different confounders.

It has been suggested that high resistin levels are related to cancer-associated chronic inflammation. Resistin exhibits potent pro-inflammatory properties by up-regulating the expression of IL-6 and TNF- α , thereby enhancing its own activity by positive feedback through the NF- κ B signaling pathway^[17]. The studies examining the association of resistin, IL-6, and TNF- α with CRC are limited in number. A few retrospective studies^[23,26,28,51,52] have reported that the resistin levels in CRC patients are higher than those in controls, and a significant positive association of resistin with CRC was demonstrated in only two studies^[23,26]. Likewise, in our case-control study, we observed significantly elevated levels of resistin in CRC patients and an association between those elevated levels and CRC risk. Previous prospective studies^[21,29,30,53] have indicated that there is no significant association between IL-6 and CRC. Although two studies, a cohort from WHI-OS^[21] and an HPFS study^[53], reported an association of IL-6 with increased risk of CRC, it was suggested that the association was likely mediated by in-

sulin^[21], and the association was observed predominantly among lean men (BMI < 25 kg/m²), as opposed to men with BMI ≥ 25 kg/m². Our results are consistent with the findings of previous case-control studies that did not find any significant association between circulating IL-6 levels and CRC risk^[39,54]. Of the published studies, only a few^[21,29,39] have examined the association of TNF-α with CRC risk and found null results. As this is the first time that we found a significant positive association between TNF-α and CRC risk, our findings should be interpreted with caution. Thus, to improve the understanding of the association of resistin, IL-6, and TNF-α with CRC, further investigation with a larger number of cases and controls and prospective studies are needed to accurately assess the possibility that circulating levels of these adipokines are associated with increased risk of CRC.

This study describes the simultaneous measurement of selected adipokines for covariate assessment to evaluate their association with CRC risk because IL-6 and TNF-α may promote tumor growth as mitogens and induce leptin and resistin production while reducing adiponectin, which stimulates growth of colon cancer cells directly or indirectly by increasing IL-6 and TNF-α. Our case-control study included a higher number of participants (100:100) than previous case-control studies (number of cases and controls less than 100). Additionally, we conducted a meta-analysis and presented the overall results of the association of adiponectin and leptin with CRC according study design; no publication bias was detected, which indicates that the results should be unbiased.

Our study has some limitations. In the case-control study, we used a single measurement of serum adipokines at baseline, which may be susceptible to short-term variation and could bias results towards the null; additionally, we did not include confounding factors such as BMI, smoking status, or alcohol consumption. Likewise, our meta-analysis was based on unadjusted OR estimates because we could not match the confounding factors due to variations in adjusted confounders among selected studies.

In summary, although the meta-analysis suggested an inverse association of adiponectin with CRC, we did not find any association in our case-control study. Leptin was inversely associated with cancer risk in our case-control study, but the meta-analysis did not support this association. In addition, the serum resistin and TNF-α, but not IL-6, were positively associated with CRC risk after adjustment of selected adipokines as covariates. In conclusion, our results do not show a causal relationship between obesity-related adipokines and colorectal cancer risk. Therefore, further studies with larger populations and prospective approach are needed to support the association between these selected adipokines and CRC.

ies have suggested an association between obesity-related adipokines and CRC risk, but prospective data are limited and the results are still inconclusive.

Research frontiers

Although several prospective and retrospective studies have demonstrated the association of various obesity-related adipokines and pro-inflammatory cytokines with CRC risk, the results are still inconclusive. To gain further insight into the association of adipokines (adiponectin, leptin, resistin) and pro-inflammatory cytokines [interleukin (IL)-6 and tumor necrosis factor (TNF)-α] with CRC risk, the authors performed a case-control study and meta-analysis.

Innovations and breakthroughs

In the present case-control study using a Korean population, adiponectin was not associated with CRC risk; however, the meta-analysis, which included our results, suggests a significant inverse association of adiponectin with CRC risk. This case-control study found an inverse association of leptin with CRC, but the results of the meta-analysis did not indicate any association. For the other adipokines, there was a positive association of resistin and TNF-α with CRC risk, but no association of IL-6 with cancer risk.

Applications

This study supports the understanding of the association of obesity-related adipokines with CRC risk, possibly representing a future strategy for large prospective studies, which may lead to improved identification of individuals at risk of developing CRC.

Peer review

This is a case-control study among 100 cancer patients with age- and sex-matched controls and a meta-analysis of currently available studies, including our study results, on the association of adiponectin and leptin with CRC. The study addresses the important topic of the association of obesity-related adipokines with CRC risk. The results are interesting and suggest that further prospective studies with a larger number of subjects are warranted.

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COMMENTS

Background

Colorectal cancer (CRC) is a leading cause of death worldwide. Previous stud-

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