RESEARCH ARTICLE

Obesity Related Adipokines and Colorectal Cancer: A Review and Meta-Analysis

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Abstract

Obesity has been considered as an important risk factor for the development of colorectal cancer (CRC), but the association has not been fully elucidated. Obesity is linked significantly to adipose tissue dysfunction and to alteration of adipokines in blood; in particular, obesity-induced inflammation is thought to be an important link between obesity and colorectal cancer. Based on epidemiological studies, we undertook a systematic review to understand the association of circulating levels of selected adipokines, including adiponectin, leptin, resistin, IL-6 and TNF-α, with the level of CRC risk. Most prospective studies suggested protective effects of adiponectin, but these were attenuated by body mass index (BMI) and waist circumference (WC) data in our meta-analysis. On the other hand, meta-analyses for leptin and CRC did not demonstrate any association, similar to the results of systematic review. Although it proved difficult to determine whether other selected adipokines (resistin, IL-6 and TNF-α) were related to CRC risk due to small number of reports, the present systematic review suggested a positive association with elevated resistin levels but null associations with IL-6 and TNF-α.

Keywords: Adipokines - colorectal cancer - obese-related adipokines - obesity - risk factors

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Introduction

Various pathophysiological mechanisms linking obesity to cancer are not completely understood, but have been postulated. Obesity induces insulin resistance and hyperinsulinaemia and increases circulating insulin levels, with this process being positively associated with colorectal cancer (CRC) risk (Gunter et al., 2008). Recent meta-analyses (Dai et al., 2007; Larsson and Wolk, 2007; Moghaddam et al., 2007) have suggested a positive association between obesity (BMI) and the CRC risk with variation of sex, cancer site and other related factors. In particular, a recent systemic review involving 93,812 CRC cases indicated that the association between BMI and CRC was stronger for men than women, for colon cancer than rectal cancer, for self-reported BMI than directly measured BMI, and for an adjustment of physical activity than a non-adjustment (Ning et al., 2010). Obesity-induced inflammation, a key feature of adipose tissue dysfunction, is thought to be an important link between obesity and the cancer development; especially, obese-related adipokines was reported several tumorigenic bioactivities (Tilg and Moschen, 2006).

Although the mechanisms of the obese-related adipokines role in CRC risk have not been fully elucidated, we suggest the possible effects of adipokines on the risk of CRC in Figure 1, based on previous reports (Bokarewa et al., 2005; Paz-Filho et al., 2011). Adiponectin may down regulate cell growth and proliferation through three different pathways: 1) blocking the activation of the signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kappa B (NF-κB) pathways by inhibiting interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α); 2) the activation of the c-AMP dependent protein kinase (AMPK) pathway to block mechanistic target of rapamycin (mTOR) and to induce anti-proliferative and pro-apoptotic effects; and 3) the suppression of sterol regulatory element-binding protein-1c (SREBP-1c) to result in low expression of fatty acid synthase (FAS) and in reduction of lipogenic activity (Paz-Filho et al., 2011). On the other hand, leptin has a tumorigenic bioactivity and regulates angiogenesis or apoptosis through several pathways; including phosphatidylinositol 3-kinase/protein-kinase B (PI3K/Akt) with the up-regulating of insulin receptor substrate (IRS), janus kinase (JAK/STAT), and the mitogenic pathway with extracellular signal regulated kinase1/2 or C-jun N-terminal kinase (ERK1/2 or JNK). Leptin also activates NF-κB resulting from the induction of inflammatory cytokines such as IL-6 (Paz-Filho et al., 2011). In addition, increased levels of resistin up-regulates inflammatory cytokines, including IL-6 and TNF-α, which can further increase the resistin levels and increase the risk of cancer via NF-κB signaling (Bokarewa et al., 2005).

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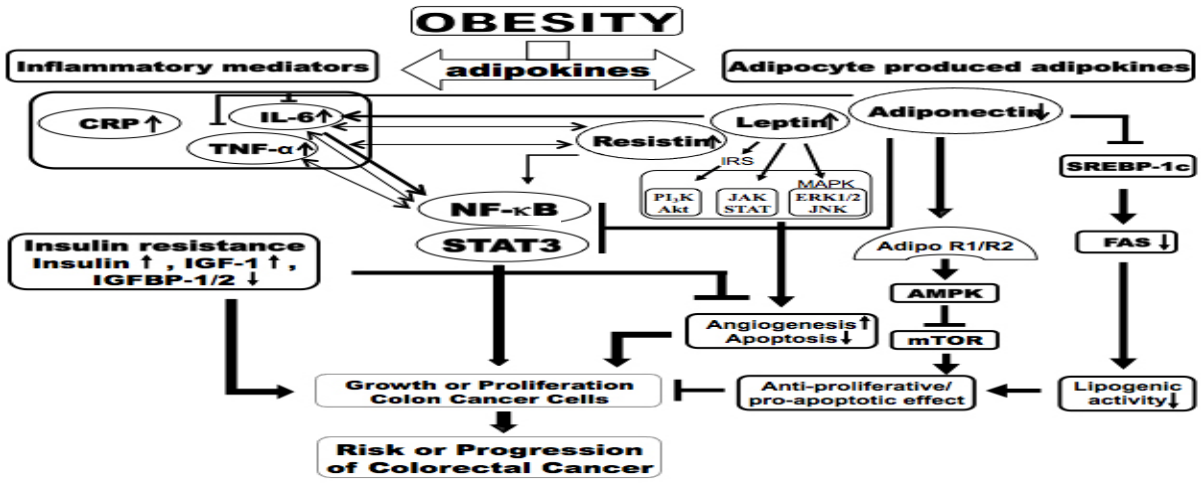

Figure 1. Hypothesis of the Biological Mechanism Linking Obesity-related Adipokines and the CRC Risk. (Modified from Paz-Filho et al., 2011 and Bokarewa et al., 2005

Several *in-vivo*, *in-vitro*, and epidemiological investigations have been reported concerning the mechanisms for the role of adipokines including adiponectin and leptin on CRC risk, and presented the significant association between obese-related adipokines and CRC risk. It is essential to perform a systematic review of observational studies on the association between CRC and the obese-related adipokines. Therefore, this systematic review aimed to provide the summary of the reported observational studies related to the association between the obese-related adipokines and CRC risk, and examined the meta-analysis for the effect of adiponectin and leptin on the cancer risk.

Materials and Methods

To provide a systematic review for addressing the association between adipokines and CRC, we used the keywords for each obese-related adipokines and pro-inflammatory adipokines and CRC from epidemiological studies using PubMed from 2002 to 2012. We searched PubMed to collect the previous literatures for the systematic review by using following search keywords: "Plasma/Serum", "each adipokines (adiponectin, leptin, resistin, IL-6, and TNF-α)", and "Colorectal cancer". We selected all prospective and retrospective studies which had been conducted to evaluate the relationship between adipokines and CRC risk and were included in our systematic review. Case-only studies, mechanism related studies, prognosis and survival studies, clinical studies, non-human studies, genetic studies, reviews and other cancer related studies were excluded. Finally, we identified total of 15 studies for adiponectin, 13 for leptin, and 7 for resistin. Although we followed the same keywords to search the studies for IL-6 and TNF-α, we did not find any additional epidemiological association studies. Thus, only 5 papers were included for the association of IL-6 and TNF-α with CRC; 2 papers from the list of adiponectin review and additional 3 were selected from the previous review paper (Aleksandrova et al., 2013).

Furthermore, we examined meta-analysis using 10 studies from 15 adiponectin reports and 9 studies from 13 leptin reports. The studies without odds ratio (ORs) or sufficient data to calculate odds ratio were excluded from this meta-analysis. Crude ORs and 95%CIs were extracted from each study to perform the meta-analysis. If the ORs were not presented but the number of cases and controls were reported, we calculated and used the crude ORs directly. Statistical heterogeneity across studies was evaluated by the χ^2 test-based Q test, (Cochran, 1954) and was considered significant heterogeneity at $p<0.05$. In this meta-analysis, we used the random-effects model (DerSimonian and Laird, 1986) instead of fixed-effects model (Mantel and Haenszel, 1959) due to variation amongst the studies in relation to characteristics of participants, and study methods and reporting. To examine the advanced analysis, we stratified by study design (prospective *vs*. retrospective). Publication Bias was assessed by Begg's (Begg and Mazumdar, 1994) and Egger's test (Egger et al., 1997). All the statistical tests were performed with the STATA Software version 10.0.

Results

Adiponectin

The anticancer properties of adiponectin can be explained, in part, by its anti-inflammatory and insulin-sensitizing effect (Kubota et al., 2002). The adiponectin-induced phosphorylation and the activation of AMPK (Yamauchi et al., 2002) have been proposed to be responsible for the increased insulin sensitivity and fatty acid oxidation in response to adiponectin treatment; however, the mechanisms underlying the insulin-sensitizing effect of adiponectin are also not completely understood. Adiponectin is an anti-inflammatory adipokine that is inversely associated with CRC risk because it inhibits cell growth and angiogenesis, suppressing the secretion of inflammatory cytokines and improving sensitivity (Barb et al., 2007). In addition to, adiponectin has been shown to inhibit the growth of macrophage precursors, suppressing mature macrophage phagocytic activities and TNF-α production *in vitro* (Yokota et al., 2000), to reduce the induction of adhesion molecules (Kawanami et al., 2004), IL-6 and IL-8, and to induce the anti-inflammatory cytokines IL-10 and the IL-1 receptor

Table 1. Epidemiogical Studies on the Association between Adiponectin and CRC Risk

Authour, Year(Ref)	Country	No. of subjects	Results	Covariates
Adiponectin				
Prospective (nested case-control)		*Case/non-case*		
Touviour et al., 2012	France (SVMA Cohort)	CRC: 50/100	One SD change of adiponectin level decreased the risk (OR=0.45, Ptrend=0.03)	Age, sex, BMI, intervention group, alcohol intake, PA, smoking, family history of CRC, WC, Height and education
Ho GY et al., 2012	USA (WHI-OS)	CRC: 457/834 women	HR Q4-Q1 = 0.65 (95% CI = 0.45-0.94; p trend= 0.015) Additionally, after adjusting for insulin level and WC, none remained significantly associated.	Age, race, smoking, history of colonoscopy, and estrogen level
Aleksandrova et al., 2012	Europe (EPIC)	CRC: 755/755 for CC/ 451/451 for RC	RR Q5-Q1=0.71, (p trend = 0.03), 0.45, (p trend<0.0001), and 0.91 (Ptrend=0.55) for total, non-HMW and HMW adiponectin respectively.The assoc. was remained only in non-HMW adiponectin with both CC (RR Q5-Q1=0.47, p trend =0.0006) and RC (RR Q5-Q1 =0.43, p trend=0.001), after stratification by site.	Age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status(reproductive factors for women, additionally)
Stocks et al., 2008	Sweden (VIP+MSP)	CRC: 125/245 men/ 181/350 women	No differnce of the adiponectin level between case and control using the Mann-Whitney U-test	
Lukanova et al., 2006	Norway (Janus Project)	CRC: 381/381 men	No association.	Leptin and C-peptide level
Wei et al., 2005	USA (MHPF)	CRC: 179/356	HR Q5-Q1=0.42 (95% CI=0.23-0.78, p trend=0.01 HR Q5-Q1=0.48 (95% CI=0.25-0.90, p trend=0.04 after adjusted BMI, additionally	Hours since last meal, family history, PA, multivitamin use, folate, vitamin D, current smoking, vitamin E, alcohol intake, aspirin use, and endoscopy before 1994
Retrospective	*Case/non-case*			
Chen et al., 2012	China	CRC: 165/102 men (71 and 94 for early and advancedstage, respectively)	Low serum adiponectin might be associated with high CC risk (p t-test=0.023)	
Gulcelik et al., 2012	Turkey	CC: 27/40	Low serum adiponectin might be associated with high CC risk (p t-test=0.023)	
Gialamas et al., 2011	Greece	CRC: 104/208	One SD change of adiponectin level among control decreased the risk (OR=0.72, p trend=0.04)	Anthropometric, demographic, and lifestyle variable as well as diabetes mellitus
Gonullu et al., 2010	Turkey	CRC: 36/37	Adiponectin levels were significantly lower in patients (p t-test=0.03), negative correlation was present between stage and adiponectin (p<0.01)	
Nakajima et al., 2010	Japan (Tokyo)	CRC: 115/115	No association with CRC	The level of resistin, leptin, visfatin, and C-peptide in blood
Kemik et al., 2010	Turkey	CC: 126/38	Adiponectin levels were significantly lower in patients (p log-rank test <0.001)	
Otake et al., 2010	Japan	CRC: 51/26 men (34 early/17 advanced)	Adiponectin was risk factor for early CRC (OR low-high=4.495, p=0.038) for low vs. high	Age, BMI, BP-S and TG
Erarslan et al., 2009	Turkey	CRC: 23/50	Adiponectin level significantly lower in CRC patients than controls (p=0.04)	
Kumor et al., 2009	Poland	CRC: 36/25	The level of adiponectin was lower in patients than controls (p t-test <0.05)	

*CRC, colorectal cancer; CC, colon cancer; RC, rectal cancer; HMW, high molecular weight; PA, physical activity; FH, family history; NSAID, nonsteroidal anti-inflammatory drugs; BMI, body mass index; WHR, waist-hip-ratio; TG, triglyceride; OR, odds ratio; RR, relative ratio; HR, hazards ratio; SVMA, Supplement of Vitamin and Mineral Antioxidants; WHI-OS, Women's Health Initiative Observational Study; EPIC, European Prospective Investigation into Cancer and Nutrition; VIP, Vasterbotten Intervention Project; MSP, Mammography Screening Project; MHPF, Male Health Professional Follow-up

antagonist (Wolf et al., 2004; Kumada et al., 2004).

Although many studies have shown that low circulating adiponectin is correlated with an increased risk of CRC (Wei et al., 2005; Aleksandrova et al., 2012; Ho et al., 2012), the association is still inconsistent (Lukanova et al., 2006; Nakajima et al., 2010). Most nested case-control studies suggested inverse association of adiponectin level with the risk of CRC, but the association was attenuated by body mass index (BMI) and waist circumference (WC) (Table 1). The results from a Supplement of Vitamin and Mineral Antioxidants (SVMA) cohort reported that a change in the adiponectin level of one standard deviation decreased the CRC risk by around 55% (Touvier et al., 2012). The inverse association was also observed in the Women's Health Initiative Observational Study (WHI-OS), but the association was not retained after an adjustment of the levels of insulin and WC (Ho et al., 2012). In a similar way to another nested case-control study (Aleksandrova et al., 2012) with 1202 cases and matched controls reported a significant inverse association between total adiponectin and CRC risk (P trend=0.03), but the association was attenuated by BMI and WC (P trend=0.23). Furthermore, non-high-molecular weight (non-HMW) adiponectin levels were associated with CRC risk (P trend<0.0001) but HMW adiponectin levels were not (P trend=0.55); also the association of non-HMW adiponectin remained significant even after stratification by site (RR=0.47 and=0.43 for colon cancer (CC) and rectal cancer (RC), respectively). Nevertheless, one prospective study demonstrated that men with the highest concentrations had approximately 60% reduced risk for CRC compared to those with the lowest

concentrations, even after adjustment for body size, WC, and physical activity (Wei et al., 2005). In contrast to prospective studies, among nine retrospective studies, only four studies have examined the association (Erarslan et al., 2009; Kumor et al., 2009; Gonullu et al., 2010; Kemik et al., 2010; Nakajima et al., 2010; Otake et al., 2010; Gialamas et al., 2011; Chen et al., 2012; Gulcelik et al., 2012). Of the four (Nakajima et al., 2010; Otake et al., 2010; Gialamas et al., 2011; Chen et al., 2012), three studies (Otake et al., 2010; Gialamas et al., 2011; Chen et al., 2012) found an inverse association between adiponectin and CRC and also suggested a protective effect of a high adiponectin level on CRC. Other case-control studies (Erarslan et al., 2009; Kumor et al., 2009; Gonullu et al., 2010; Kemik et al., 2010; Gulcelik et al., 2012) compared the mean levels of adiponectin between cases and controls, finding that the levels of adiponectin in CRC patients were lower than those in healthy controls (Table 1).

Recently, a meta-analysis of 13 observational studies (Xu et al., 2011) (including 3 prospective and 10 retrospective studies) demonstrated markedly lower adiponectin values in patients and reported weighted mean differences (WMD) between patients and controls of -1.084 μg/ml, (p=0.005) for CRC, supported by another meta-analysis (WMD=-1.51 and -1.29) (An et al., 2012). Those meta-analyses suggested significantly inverse association between CRC and blood adiponectin level, but it is necessary to consider the study design and sample size in interpretation of the association. Although we did not observe any association of adiponectin with CRC, after stratification by study design, an inverse association was observed in prospective study with significant heterogeneity (OR=0.716, 95%CI: 0.606-0.847, test for heterogeneity p=0.105) in our meta-analysis (Figure 2a). Begg's and Egger's test showed that there was no statistical significance for the evaluation of publication bias (data not shown).

Leptin

Circulating serum leptin levels parallel adipose tissue amounts and is substantially increased in the obese (Considine et al., 1996); therefore, the leptin mechanism is related to the regulation of body weight, appetite, and metabolism (Friedman and Halaas, 1998). It is also synthesized by pre-adipocytes, especially when these are stimulated in paracrine way by the proinflammatory cytokines secreted by macrophages infiltrating the adipose tissue (Simons et al., 2005). Leptin binds to its receptor (LR) and activates different signaling pathways, such as JAK/STAT, MAPK, PI3K/Akt, AMPK and IRS (Fruhbeck, 2006), which promotes angiogenesis and enhances the pathogenesis of CRC (Sierra-Honigmann et al., 1998). Leptin may promote tumor growth by acting as mitogens for normal and neoplastic colon cells and by inhibiting apoptosis (Ho et al., 2012). Leptin regulates several neuroendocrine axes, some of which play important roles in the pathogenesis of female CRC (Tamakoshi et al., 2005).

Among seven nested case-control studies (Stattin et al., 2003; Stattin et al., 2004; Tamakoshi et al., 2005; Stocks et al., 2008; Aleksandrova et al., 2012; Ho et al., 2012; Touvier et al., 2012), four studies reported a positive association between elevated leptin levels and the CRC risk (Stattin et al., 2003; Stattin et al., 2004; Tamakoshi et al., 2005; Ho et al., 2012). Although earlier reports observed a risk effect of high leptin levels on CRC (Tamakoshi et al., 2005; Stattin et al., 2003; Stattin et al., 2004), recent reports (Aleksandrova et al., 2012; Touvier et al., 2012) did not support the association with the exception of one study in the USA (Ho et al., 2012). The result from a WHI-OS female cohort with 457 cases and 834 non-cases showed a significantly positive association between elevated leptin levels and CRC; however, the association was attenuated by WC and insulin, indicating that the link may be explained by hyper-insulinemia (Ho et al., 2012). A European Prospective Investigation into Cancer and Nutrition (EPIC) cohort with a much larger number of cases provided a more accurate adjustment for obesity indices including WC for abdominal obesity, but did not find any association between leptin levels and CRC (Aleksandrova et al., 2012). Due to the close biological

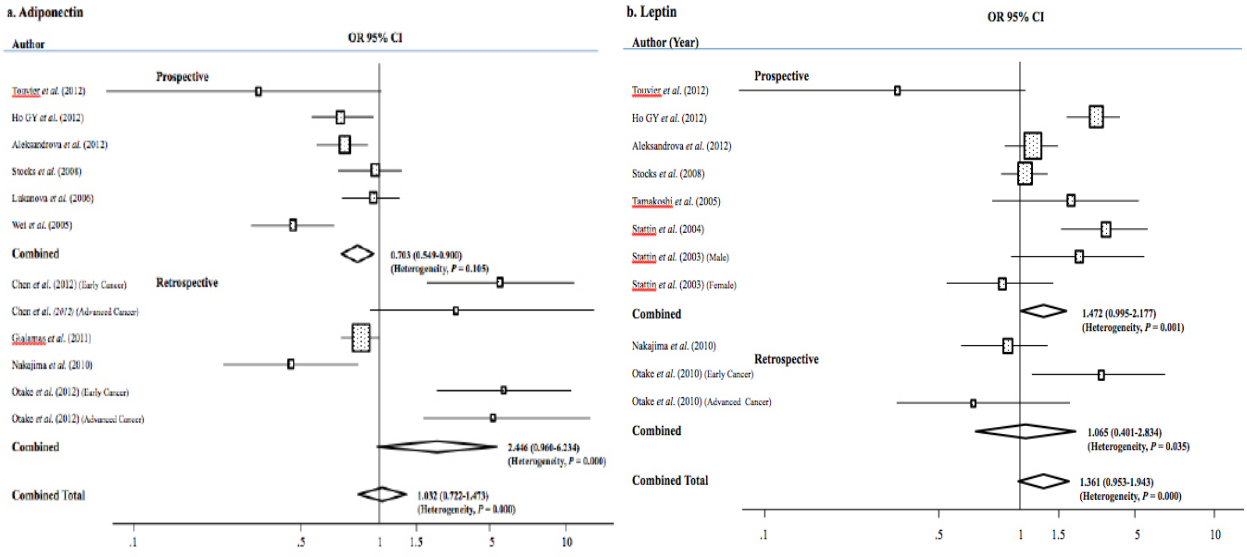

Figure 2. Meta-analysis for the Association of Adiponectin and Leptin with Colorectal Cancer Risk

Table 2. Epidemiogical Studies on the Association of Leptin and Resistin with CRC Risk

Authour, Year	Country	No. of subjects	Results	Covariates
Leptin				
Prospective (nested case-control)		*Case/non-case*		
Touvier et al., 2012	France (SVMA Cohort)	CRC: 50/100	No differnce of the leptin level between case and control using the Student t-test	Age, sex, BMI, intervention group, alcohol intake, PA, smoking, family history of CRC, WC, Height and education
Ho GY et al., 2012	USA (WHI-OS)	CRC: 457/834 women only	HR Q4-Q1=2.50 (p trend<0.001)/1.76 (p trend=0.068) after adjusted WC, additionally	Age, race, smoking, history of colonoscopy, and estrogen level
Aleksandrova et al., 2012	Europe (EPIC)	CRC: 713/713 for CC/ 416/416 for RC	No association	Age, sex, study center, follow-up time since blood collection, time of the day at blood collection and fasting status (reproductive factors for women, additionally)
Stocks et al., 2008	Sweden (VIP+MSP)	CRC: 125/245 men/ 181/350 women	No differnce of the leptin level between case and control using the Mann-Whitney U-test. No association between leptin and CRC	BMI
Tamakoshi et al., 2005	Japan (JCC)	CRC: 58/145 women (study area and age matched control)	RR Q2&Q3-Q1=1.25(95%CI=0.46-3.39) and RR Q4&Q5-Q1=3.12(95%CI=1.15-8.47)	BMI at baseline, smoking, alcohol consumption, PA, beef intake, green leafy veg., FH of CRC, parity, age at menarche, menopausal status, IGF-1, IGF-II and IGFBP-3
Stattin et al., 2004	Norway (Janus Biobank)	CRC: 235/378 CC/ 143/378 RC men	RR Q4-Q1=2.77(95%CI = 1.44-5.12, p trend=0.007) for CC, especially for left CC (RR Q4-Q1=3.78, p trend=0.007)	C-peptide
Stattin et al., 2003	Sweden (NSHD)	CRC: 75/142 men 93/185 women	CRC increased in men with the increasing level of leptin (OR other quartile-Q1 = 2.28)	BMI, insulin, and smoking. Used matched control for age, sex, date of blood sampling and fasting status
Retrospective	*Case/non-case*			
Salageanu et al., 2010	Bucharest (Romania)	CC: 29/27	Low leptin in patients than controls; both before (p Wilcoxon signed-rank test=0.01) and after (p Wilcoxon signed-rank test<0.01) surgery. A statistically significant decrease of leptin concentration was noted after surgery as compared to pre-surgical level (p Wilcoxon signed-rank test<0.01)	
Nakajima et al., 2010	Japan	CRC 115/114	No association	
Otake et al., 2010	Japan	CRC: 51/26 (34 early/17 advanced cancer)	Leptin level was not significant risk factor for the early and advanced cancer	Age, BMI, BP-S, TG, and adiponectin
Kemik et al., 2010	Turkey	CC 126/38	Leptin level was significantly higher in patients (p log-rank test<0.001)	
Kumor et al., 2009	Poland	CC 36/25	Low level of leptin in CC patients (p<0.05) than controls	
Arpaci et al., 2002	Turkey	CC 36/36	Leptin level of CRC were significantly lower than those of the controls (p=0.003) No differences of level between early and advanced stage patients	
Resistin				
Prospective (nested case-control)		*Case/non-case*		
Ho GY et al., 2012	USA (WHI-OS)	CRC 457/834 women	Not observed any association.	Age, race, smoking, history of colonoscopy, and estrogen level
Retrospective	*Case/non-case*			
Danese et al., 2012	Italy	CRC 40/40	Resistin resulted to be an independent predictor of CRC (OR continuous =1.331, 95% CI = 1.030-1.719, P = 0.020), after adjusted all covariates	Age, sex, BMI, and lifestyle parameters
Nakajima et al., 2010	Japan (Tokyo)	CRC 115/115	Resistin level was significantly higher in the colorectal cancer patients than controls (OR=2.067, p=0.03), and gradually increased with tumor stage (p<0.01)	Used age-, sex, and BMI-matched control. The level of adiponectin, leptin, visfatin, and C-peptide in blood
Salageanue et al., 2010	Bucharest (Romania)	CC 29/27	Resistin levels in CC patients were significantly higher as compared to controls, both pre- and post-operatively (p Wilcoxon signed-rank test <0.001).	
Gonullu et al., 2010	Turkey	CRC 36/37	Resistin level in CRC patients are higher than those in controls.No association	
Otake et al., 2010	Japan	CRC 51/26 men (34 early/17 advanced)	Resistin level in CRC patients are higher than those in controls. No association	Age, BMI, BP-S and TG
Kumor et al., 2009	Poland	CRC 36/25	Resistin level in CRC patients are higher than those in controls. No association	

*JACC, Japan Collaborative Cohort; NSHD, Northern Sweden Health & Disease

relationship between adiposity and leptin, it is difficult to separate independent effects; possible colinearities between two factors should be considered when interpreting the results.

Only two reports from six case-control studies (Arpaci et al., 2002; Kumor et al., 2009; Kemik et al., 2010; Salageanu et al., 2010; Nakajima et al., 2010; Otake et al., 2010), have conducted association analysis, but did not observe any association between leptin and CRC (Nakajima et al., 2010; Otake et al., 2010). Among other four studies, three showed significant low leptin levels in CRC patients, which is independent of weight loss compared to controls (Arpaci et al., 2002; Kumor et al., 2009; Salageanu et al., 2010). Among them, a case-control

Table 3. Epidemiogical Studies on the Association of IL-6 and TNF-α with CRC Risk

Authour, Year (Ref)	Country	No. of subjects	Results	Covariates
IL-6				
Prospective (nested case-control) Case/non-case				
Ho GY et al., 2012	USA (WHI-OS)	CRC 457/834 women	HR Q4-Q1 = 1.14 (95% CI = 0.97-2.06; P trend = 0.043). Additionally, after adjusting for insulin level and WC, none remained significantly associated	Age, race, smoking, history of colonoscopy, and estrogen level
Heikkila et al., 2009	UK (BWHHS+Caerphilly cohort)	CRC: 32/3074 in 30/845 in Caerphilly cohort	Not found any association between IL-6 level and CRC	Age, BMI, smoking, PA, HRT use and NSAID use
Il'yasova et al., 2005	USA (HABC)	CRC 40/2169	HR continuous = 1.44 (95% CI = 0.90-2.31)	Age, gender, race and site
Retrospective study	Case/control			
Chan et al., 2011	USA	CRC 280/555 women	No association	Age at blood draw, date of blood draw, BMI, PA, smoking, menopause, current postmenopausal hormone use, prior lower gastrointestinalendoscopy, FH, regular multivitamins, NSAID use, energy intake, servings of beef, pork, or lamb as a main dish, and alcohol consumption
Kemik et al., 2010	Turkey	CC 126/38	Not observed any association High levels of IL-6 in patients than controls (p<0.001)	
TNF-a				
Prospective (nested case-control) Case/non-case				
Ho GY et al., 2012	USA (WHI-OS)	CRC 457/834 women	Not observed any association	Age, race, smoking, history of colonoscopy, and estrogen level
Il'yasova et al., 2005	U. S.	CRC 296/2169	HR continuous=0.90 (95%CI=0.42-1.94)	Age, gender, race and site
Retrospective study Case/control				
Kemik et al., 2010	Turkey	CC 126/38	Not observed any association High levels of TNF-α in patients than controls (P<0.001)	

*HABC, Health Aging and Body Composition study; BWHHS, British Women's Heart and Health Study

study (Salageanu et al., 2010) suggested that leptin levels may gradually decreases with tumor aggressiveness resulting low leptin in advanced stages of CRC. Similarly, other two retrospective studies included high percentage of advanced stages of CRC cases 58.33% (Arpaci et al., 2002) and 55.56% (Kumor et al., 2009). Thus, it can be speculated that patients with advanced stage of CRC may experience weight loss which may cause low leptin level in blood; however further studies are needed to elucidate mechanism of decreasing leptin level in CRC. On the other hand, one case-control study (Kemik et al., 2010) with 126 cases observed that leptin levels were significantly higher in patients with CRC, but the cases suffered from cachexia (Table 2).

Our present meta-analysis did not observe any significant association between leptin and CRC either after stratification by study design, which is consistent to the result from a recent meta-analysis (Gialamas et al., 2013). Although significant heterogeneity was observed between studies (Q test p=0.000 for overall, Q test p=0.001 for prospective, and p=0.035 for retrospective studies), the heterogeneity could not be explored by meta-regression as few studies were included in the meta-analysis (GS, 2011) (Figure 2b). No publication bias has shown according to the Begg's and Egger's test (data not shown). Thus, for the prediction of overall association result of leptin on CRC risk, large and well-designed studies are warranted.

Resistin

Resistin, a 12.5-kDa protein hormone, is a newly discovered member of cysteine-rich proteins secreted from adipose tissue, and is associated with insulin resistance (Nagaev and Smith, 2001). Resistin is reportedly involved in the process of inflammation, showing up-regulation of IL-6 and TNF-α and enhancing its own activity by a positive feedback mechanism mediated through the NF-ϰB signaling pathway (Salageanu et al., 2010). Resistin is secreted from adipose tissue and monocytes/macrophages and is correlated with the levels of inflammatory cytokines (Gonullu et al., 2010). Recent data indicate that the stimulation of macrophages in vitro with endotoxin or proinflammatory cytokines leads to a marked increase in resistin production and, vice versa, resistin strongly up-regulates IL-6 and TNF-α production (Bokarewa et al., 2005). In a human study, experimental endotoxemia induced a dramatic rise in circulating resistin levels, supporting inflammation as a hyper resistinemic state (Reilly et al., 2005). Because chronic low-grade systemic inflammation increases the risk of cancer (Lee et al., 2011), the finding of higher resistin levels in CRC patients may be explained by the activation of monocytes as a part of the generalized inflammatory process. Danese et al. (2012) suggested that resistin may indeed present a molecular link between inflammation and CRC carcinogenesis (Danese et al., 2012).

A recent prospective study has examined the association between resistin and CRC, but could not observe any significant result (Ho et al., 2012). Two case-control studies (Nakajima et al., 2010; Danese et al., 2012) showed an association between high levels of resistin and CRC risk. A study with 40 cases and matched controls (Danese et al., 2012) demonstrated a positive association between serum resistin levels and CRC risk, also showing that these levels gradually increased with the progression of the tumor stage (p=0.042) supported by the results of Nakajima et al. (Nakajima et al., 2010) (p=0.03). In particular, Nakajima et al. observed that resistin levels were significantly higher than those in controls independent of the BMI and gradually increased with progression to the tumor stage (Nakajima et al., 2010). These findings imply that resistin is a biomarker associated with

colorectal malignant potential and stage progression. On the other hand, four case-control studies (Kumor et al., 2009; Otake et al., 2010; Gonullu et al., 2010; Salageanu et al., 2010) observed only that circulating resistin levels were significantly increased in CRC patients while not finding an association with CRC risk. Besides, a study conducted by Salageanu et al. (Salageanu et al., 2010) did not find any correlation between the serum levels of resistin and tumor stage, localization or grade of differentiation, although colon cancer patients displayed increased serum resistin levels. This discrepancy may be explained by the limited number of patients in advanced stages of disease (n=8) (Table 2).

Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)

Obesity is associated with chronic low-grade inflammation due to the production of pro-inflammatory cytokines, such as IL-6 and TNF-α, which induce the hepatic secretion of acute phase protein, such as C-reactive protein (CRP) (Roberts et al., 2010). IL-6 is one of the major pro-inflammatory cytokine released from adipose tissue (Eder et al., 2009) and elevated in the obese individuals (Fantuzzi, 2005). Both its expression in adipose tissue and the circulating concentration are positively correlated with obesity and insulin resistance (Fernandez-Real and Ricart, 2003). It appears to enhance tumorigenesis by paracrine and autocrine mechanism to stimulate cell growth and inhibit apoptosis (Lotem and Sachs, 1998). A recent review of studies concluded that serum IL-6 levels were found to have increased in patients with CRC; and these elevated levels of IL-6 were associated with increasing tumor stages and tumor size, with metastasis and decreased survival (Knupfer and Preiss, 2010). TNF-α is also found to be increased with obesity and correlate positively with BMI (Cottam et al., 2004). Studies suggested that TNF-α is the most important mediators of inflammation which is involved in obesity-related insulin resistance (Kern et al., 2001). It is also involved in the production of reactive oxygen species (ROS) that are important in cell proliferation or cell survival (Pais et al., 2009).

Among three prospective studies (Il'yasova et al., 2005; Heikkila et al., 2009; Ho et al., 2012) that have investigated circulating IL-6 in relation to CRC risk, two studies did not observe an association between IL-6 and CRC (Il'yasova et al., 2005; Heikkila et al., 2009); however, WHI-OS (Ho et al., 2012) reported that high levels of IL-6 were positively associated with the risk of CRC, which likely to be mediated by insulin. For the case-control studies, just two studies were reported; one study (Chan et al., 2011) has shown no association, but another found significant high level of IL-6 in CRC patients compared to controls ($p<0.001$) (Kemik et al., 2010). Two prospective studies for the association between circulating TNF-α and CRC risk (Il'yasova et al., 2005; Ho et al., 2012) did not observe any association between TNF-α and CRC. Similarly, no association was observed in a case-control study, even the level of circulating TNF-α were significantly higher in cases than controls ($p<0.001$) (Kemik et al., 2010) (Table 3).

Discussion

In conclusion, since the effect of adipokines on the risk of CRC have been suggested and reported by several researchers, many studies examined the association between adipokines and CRC risk using population-based studies. This review indicates that adiponectin levels in patients with CRC are significantly lower than those in healthy controls, which suggested that adiponectin may be involved in the development of colorectal tumor. In particular, the negative dose response relationship between circulating adiponectin level and the CRC risk was observed in many prospective studies. Additionally, in the present meta-analysis, the effects of estimates were consistently stronger in large-scale studies and prospective studies. However, it must be interpreted with more caution because the effect may be weaker or attenuated than indicated by each considerable conditions including study design, sample size, the kind of obese criteria (BMI *vs*. WC), gender, and adiponectin form (HMW *vs*. non-HMW etc.). In addition to, alcohol, diet, exercise or medication use may also alter adiponectin level and residual confounding may still be present (Xu et al., 2011). On the other hand, leptin levels were positively correlated with CRC in some prospective studies (Stattin et al., 2003; Stattin et al., 2004; Tamakoshi et al., 2005), but not in others. (Nakajima et al., 2010; Aleksandrova et al., 2012) It is questionable whether leptin is a cause or mere bystander, since leptin is not as strongly associated with CRC in women, who have much higher leptin than men. Moreover, results from recently published meta-analysis (Gialamas et al., 2013) and our present meta-analysis did not observe any significant association of leptin with CRC. Paradoxically, some studies observed significantly low serum leptin concentration in patients with colorectal tumors independent of BMI and weight loss (Arpaci et al., 2002; Kumor et al., 2009). Studies with the information so far, it appears that the association studies with CRC were in limited numbers for resistin, IL-6 and TNF-α; however, higher levels of resistin and IL-6 were consistently found in CRC patients than healthy controls. Therefore, further research with more evidence from large-scale prospective studies is needed to improve the understanding of these associations.

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