RESEARCH ARTICLE

Lack of any Prognostic Relationship between Adiponectin Receptor (Adipo R1/R2) Expression for Early/ Advanced Stage Gastric Cancer

Talat Ayyildiz[1]*, Enver Dolar[2], Nesrin Ugras[3], Oguzhan Sitki Dizdar[4], Saduman Balaban Adim[3], Omer Yerci[3]

Abstract

Introduction: Adiponectin (ApN) is a complement C1q-related protein, mainly secreted from adipose tissue, that signals through ApN receptor1 (Adipo-R1) and ApN receptor 2 (Adipo-R2). Low serum ApN concentrations are associated with obesity-related malignancies. However, there are very few studies on any prognostic role of ApN receptors in gastric cancer. Objectives: The aim of this study is to investigate the relationship between AdipoR1/R2 expression and early/advanced stage gastric cancer in terms of clinicopathologic characteristics and survival. Materials and Methods: Eighteen patients with early and 39 with advanced stage gastric cancer who underwent surgical gastric resection were included in this study. Results: Adipo-R1 expression was low in 2 of the 18 patients with early stage gastric cancer (11.1%), while 4 had low Adipo-R2 expression (22.2%). In those with advanced stage gastric cancer, 7 of 39 had low Adipo-R1 expression (17.9%) and 16 had low Adipo-R2 expression (41%). Adipo-R2 expression was significantly higher (p=0.011) in moderately differentiated tumors when compared to well-differentiated tumors. While there was nearly a statistically significant relationship between TNM stage (T, tumor size; N, regional lymph node; M, whether distant metastases exist) and Adipo-R2 expression (p=0.054), there was no relationship between Adipo-R1/-R2 expression with tumor stage and survival. Conclusion: Adipo-R1/-R2 expression has no prognostic significance of in early/advanced stage gastric cancer.

Keywords: Adiponectin - Adipo R1 - Adipo R2 - gastric carcinoma - survival - prognosis

Asian Pac J Cancer Prev, **15 (11)**, 4711-4716

Introduction

Adiponectin (ApN, 30 kDa) is a complement C1q-related protein that is mainly secreted from adipose tissue (Maeda et al., 1996). It is present in two forms, which include full length ApN (fAdipo) and biologically active globular ApN (gApN) (Kadowaki and Yamauchi 2005).

It has been shown that ApN levels decrease in some conditions, such as insulin resistance and hyperinsulinemia (Diez and Iglesias 2003). ApN exhibits antiatherogenic effects by inhibiting vascular smooth muscle and endothelial cells (Yokota et al., 2000; Arita et al., 2002). In addition, ApN induces antiangiogenesis and has antitumoral effects (Brakenhielm et al., 2004; Ishikawa et al., 2007; Ogunwobi and Beales 2008). It has been reported that the concentration of ApN is low in obese patients (Cnop et al., 2009). Therefore, there may be a relationship between low ApN concentration and obesity-related malignancies (Joshi and Lee, 2014).

It has also been reported that there are reduced serum concentrations of ApN in gastric, esophageal, colorectal and endometrial cancers (Fenoglio et al., 2000; Mantzoros et al., 2004; Dal Maso et al., 2004; Ogunwobi and Beales 2008; Ishikawa et al., 2005; Gulcelik at al., 2012).

ApN signals through ApN receptor1 (Adipo-R1) and ApN receptor 2 (Adipo-R2) (Yamauchi et al., 2003). ApN receptors have been implicated in various cancers, including prostate, breast, and endometrial cancer (Otani et al., 2010). The expression of these receptors has also been implicated in gastric cancer and in patients who underwent immunohistochemical surgical resection (Ishikawa et al., 2007; Barresi et al., 2009).

As the grade of renal cell cancer increases, the serum ApN levels decrease, and metastatic tumors tend to express lower Adipo-R2 (Pinthus et al., 2008). Serum ApN levels are lower in patients with advanced stage lung cancer than in those with local lung cancer (Petridou et al., 2007). Otani and colleagues hypothesized that ApN receptors would be downregulated in the early stages of cancer development in cancer cells that are protected from the antiproliferative effects of ApN (Otani et al., 2010). Based on these data, it has been hypothesized that

*[1]Department of Gastroenterology, Faculty of Medicine, Ondokuz Mayis University, Samsun, [2]Department of Gastroenterology, [3]Department of Pathology, [4]Department of Internal Medicine, Faculty of Medicine, Uludag University, Bursa, Turkey &Equal contributors *For correspondence: talatayy@gmail.com*

Adipo-R1 and Adipo-R2 may have prognostic significance in early stage and advanced stage gastric cancer. In this study, we investigate the clinicopathologic characteristics, survival, and the relationship between Adipo-R1 and Adipo-R2 expression (immunohistochemically) in cases with early stage and advanced stage gastric cancer and in those who underwent surgical resection. The significance of Adipo-R1 and Adipo-R2 expression in tumor aggression is evaluated.

Materials and Methods

The patients who underwent surgical gastric resection were enrolled from the archives of a local university hospital. Eighteen patients (8 female, 10 male, median age 58.33±15.83 years) with early stage gastric cancer and 39 patients (10 female, 29 male, median age 63.38±10.27 years) with advanced stage gastric cancer were included in this study.

Tumors confined to the mucosa and submucosa were considered to be early stage gastric cancer, while any infiltration beyond the submucosa was considered to be advanced stage gastric cancer. All patients were graded and staged histologically according to the World Health Organization (WHO) and TNM system. For statistical analyses, the patients with mucinous and signet ring cell were grouped and compared to those with tubular ones. A statistical analysis comparing pTNM1 and pTNM2 with pTNM3 and pTNM4 was conducted. Follow-up length ranged from 1 month to 84 months (mean for early stage gastric carcinoma: 38.28±31.90 months, mean for advanced stage gastric cancer: 21.03±15.77 months). This study was approved by the local ethics committee.

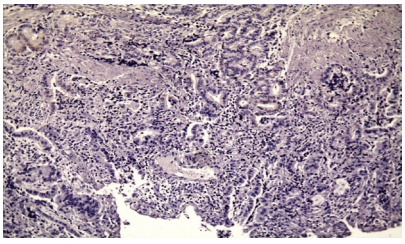

Figure 1. Adipo R1 Negative- Tumor Tissue (DAB X 400)

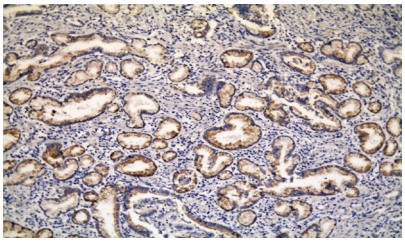

Figure 2. Adipo R1 Positive- Tumor Tissue (DAB X 400)

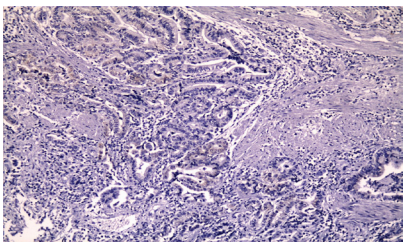

Figure 3. Adipo R2 Negative-Tumor Tissue (DAB X 400)

Immunohistochemistry

Adiponectin receptor 1 and adiponectin receptor 2 expression in tissues was determined by immunohistochemical staining. Adipo-R1 and Adipo-R2 (ab126611 and ab77612, respectively; Abcam, Inc., Cambridge, MA, USA; working dilution 1/250) were used as the primary antibodies. A streptavidin-avidin-biotin method was used for immunohistochemical staining as follows. Four-micron thick sections were deparaffinized in an oven overnight at 60°C. The sections were dipped three times in Xylene for 5 minutes each and three times in 96% citrate buffer (pH 6.0) for 5 minutes each. Then, they were boiled in a 750 Watt microwave oven with distilled water at 5 minutes intervals for a total of 20 minutes. After incubation for 20 minutes at room temperature, they were washed 2 times with PBS. The sections were dried, and then were incubated for 15 minutes in a 25°C humid chamber with 3% hydrogen peroxide. They were again washed with PBS and kept 10 minutes in protein blocking solution. The sections were incubated for 1 hour with primary antibody, and then washed twice with PBS for 3

Table 1. Clinicopathological Characteristics of Patients with Gastric Cancer

Charateristics		Early stage gastric carcinoma	Advanced stage gastric carcinoma
Age (median)		58.3+15.8	63.3+10.2
Sex	Female	8 (44.4%)	10 (55.6)
	Male	10 (25.6)	29 (74.4)
Median follow-up time (months)		38.2+31.8	21.0+15.7
Tumor localization	Cardia	2 (11.1)	10 (25.6)
	Corpus	10 (55.5)	15 (38.5)
	Antrum	6 (33.3)	14 (35.9)
Tumor size	<5cm	14 (77.8)	17 (43.6)
	>5cm	4 (22.2)	22 (56.4)
T stage	pT1	18 (100.0)	0 (0.0)
	pT2	0	3 (7.7)
	pT3	0	30 (76.9)
	pT4	0	6 (15.4)
N stage	N0	15(83.3)	8 (20.5)
	N1	1 (5.6)	4 (10.3)
	N2-N3	2 (11.2)	27 (69.2)
Pathological Stage (TNM)	I	18 (100)	1 (2.6)
	II	0	8 (20.5)
	III	0	28 (71.8)
	IV	0	2 (5.1)
Histopathology	Tubular	13(72.2)	31 (79.5)
	Mucinosis	1(5.6)	5 (12.8)
	Signet ring	4 (22.2)	3 (7.7)
Histological Differentiation	Well	10 (55.6)	1(2.6)
	Mild	3 (16.7)	19 (48.7)
	Poor	5 (27.8)	19 (48.7)
H. pylori	Not Exist	14 (77.8)	33 (84.6
	Exist	4 (22.2)	6 (15.4)
Perineural invasion	Not Exist	18 (100.0)	14 (35.9)
	Exist	0 (0.0)	25 (64.1)
Lymphatic invasion	Not Exist	16 (88.9)	17 (43.6)
	Exist	2 (11.1)	22 (56.4)
Venovascular invasion	Not Exist	18 (100.0)	35 (89.7)
	Exist	0 (0.0)	4 (10.3)
Adipo R1 expression	Not Exist	16 (88.9)	32 (82.1)
	Exist	2 (11.1)	7 (17.9)
Adipo R2 expression	Not Exist	14 (77.8)	23 (59)
	Exist	4 (22.2)	16 (41.0)

minutes each. After 15 minutes in the secondary antibody (Biotinylated Link), they were washed with PBS and then put in DAB chromogen for 10 minutes.

The sections were washed with distilled water and evaluated by light microscopy according to the prevalence and severity of staining. The preparations having significant staining in the tissue were considered to be positive (Figure1, 2, and 3).

Statistical analysis

Descriptive statistics were calculated for all of the study data. The Kolmogorov - Smirnov test was used to determine whether the continuous variables satisfied the normality assumption.

The Mann Whitney U test was used to compare all variables between groups. A Pearson's chi-square test was used for the comparison of categorical variables. A correlation test was used to examine the relationships between variables, and a value of $p<0.05$ was considered statistically significant. A Kaplan-Meier analysis and a log rank test were used to compare survival time (stage age etc.) distributions. All analyses were performed with the SPSS 13.0 package program.

Results

There was no significant difference between the expression of adiponectin receptor 1 and adiponectin receptor 2 in patients with early stage and advanced stage gastric cancer. The patients' demographic data are presented in Table 1. Eighteen (8 female, 10 male) of the cases had early stage gastric carcinoma, and 39 (10 female, 29 male) had advanced stage gastric carcinoma. There were significant differences between those with early stage and advanced stage gastric cancer in terms of T stage, N stage, TNM stage, histological differentiation, and perineural and lymphatic invasion. The expression of Adipo-R1 and Adipo-R2 was poor in both groups (p=0.510, p=0.167, respectively). In addition, there were no significant relationships between Adipo-R1 and Adipo-R2 expression and age, sex, tumor location, tumor size, lymph node involvement, TNM stage, early and advanced stage gastric cancer, histologic subtypes, differentiation, *Helicobacter pylori* infection, or perineural, lymphatic, and venovascular invasion. There was no significant relationship between Adipo-R1 and Adipo-R2 expression in terms of overall survival and

Table 2. The Relationship between the Clinicopathological Characteristics of Patients with Gastric Cancer and Adiponectin Rreceptor 1 and 2 Expression

		AdipoR1			AdipoR2		
		Negative (n=48)	Positive (n=9)	p value	Negative (n=37)	Positive (n=20)	p value
Age		62.2+12.5	59.1+27.7	0.65	61.35+13.3	62.60 +10.7	0.22
	<65	26 (54.2)	6 (66.7)	0.71	21 (56.8)	11 (55.0)	0.89
	≥65	22 (45.8)	3 (33.3)	16 (43.2)	9 (45.0)		
Sex	Female	14 (29.2)	4 (44.4)	0.44	13 (35.1)	5 (25.0)	0.43
	Male	34 (70.8)	5 (55.6)	24 (64.9)	15 (75.0)		
Survival	Alive	23 (47.9)	2 (22.2)	0.14	15 (40.5)	10 (50.0)	0.49
	Dead	25 (52.1)	7 (77.8)	22 (59.5)	10 (50.0)		
Location	Cardia	9 (18.8)	3 (33.3)		8 (21.6)	4 (20.0)	0.19
	Body	23 (47.9)	2 (22.2)		19 (51.4)	6 (30.0)	
	Antrum	16 (33.3)	4 (44.4)		10 (27.0)	10 (50.0)	
Tumor Size	<5cm	27 (56.3)	4 (44.4)	0.71	21 (56.8)	10 (50.0)	0.62
	≥5 cm	21 (43.8)	5 (55.6)	16 (43.2)	10 (50.0)		
pT	T1-T2	18 (37.5)	3 (33.3)	1.00	15 (40.5)	6 (30.0)	0.43
	T3-T4	30 (62.5)	6 (66.7)	22 (59.5)	14 (70.0)		
pN	N0	20 (41.7)	3(33.3)	0.72	18 (48.6)	5 (25.0)	0.08
	N1-N2-N3	28 (58.3)	6 (66.7)	19 (51.4)	15 (75.0)		
TNM stage	1-2	23 (47.9)	4 (44.4)	1.00	21 (56.8)	6 (30.0)	0.05
	3-4	25 (52.1)	5 (55.6)	16 (43.2)	14 (70.0)		
Tumor type							
Early stage gastric cancer		16 (33.3)	2 (22.2)	0.70	14 (37.8)	4 (20.0)	0.16
Advanced stage gastric cancer		32 (66.7)	7 (77.8)	23 (62.2)	16 (80.0)		
WHO histotype							
Tubular		37 (77.1)	7 (77.8)	1.00	27(73.0)	17 (85.0)	0.34
Mucinous- signet ring		11 (22.9)	2 (22.2)	10 (27.0)	3 (15.0)		
Histological grade	Well	10 (20.8)	1 (11.1)		9 (24.3)	2 (10.0)	0.01
	Mild	17 (35.4)	5 (55.6)		9 (24.3)	13 (65.0)	
	Poor	21 (43.8)	3 (33.3)		19 (51.4)	5 (25.0)	
H. pylori	Not Exist	40 (83.3)	7 (77.8)	0.65	30 (81.1)	17 (85.0)	1.00
	Exist	8 (16.7)	2 (22.2)	7 (18.9)	3 (15.0)		
Perineural invasion	Not Exist	29 (60.4)	3 (33.3)	0.161	24 (64.9)	8 (40.0)	0.07
	Exist	19 (39.6)	6 (66.7)	13 (35.1)	12 (60.0)		
Lymphatic invasion	Not Exist	26 (54.2)	7 (77.8)	0.27	20 (54.1)	13 (65.0)	0.42
	Exist	22 (45.8)	2 (22.2)	17 (45.9)	7 (35.0)		
Venous invasion	Not Exist	44 (91.7)	9 (100.0)	1.00	33 (89.2)	20 (100.0)	0.28
	Exist	4 (8.3)	0 (0)	4 (10.8)	0 (0.0)		

progression free survival (Figure 4 and 5).

The clinicopathologic characteristics of the patients are shown in Table 1. In early stage gastric cancer, Adipo-R1 expression was present in 2 of 18 patients (11.1%), and Adipo-R2 expression was present in 4 of 18 (22.2%) patients. In those with advanced stage gastric cancer, Adipo-R1 expression was present in 7 of 39 patients (17.9%), and Adipo-R2 expression was present in 16 of 39 patients (41%). The relationship between TNM stage and Adipo-R2 expression was nearly significant (p=0.054) (Table 2). In terms of histologic grade, Adipo-R2 expression was significantly higher in moderately differentiated tumors when compared to well-differentiated tumors (p=0.011).

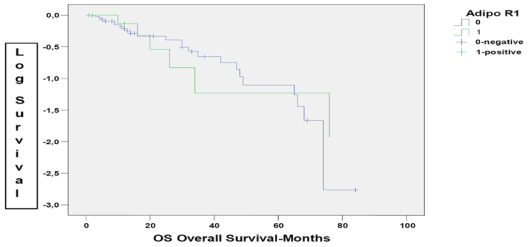

Figure 4. Analysis of Overall Survival (Adipo R1)

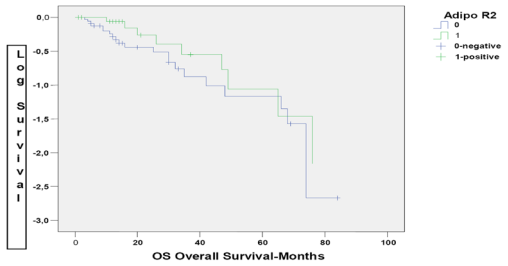

Figure 5. Analysis of Overall Survival (Adipo R2)

Tumor stage (pT1+pT2/pT3+pT4) was identified as the determining factor (p=0.004) for both overall survival and disease-free survival. Only venovascular invasion was statistically significant (p=0.018) in overall survival analysis (Table 3). Although none of the variables were significant in progression free survival analysis, perineural invasion came close (p=0.052).

Discussion

Adiponectin is an adipokine that is abundant in the circulation and has contradictory functions and multiple features in tumorigenesis. These multiple and complex roles include metabolic regulation, changes in the tumor microenvironment, and direct effects on cancer cells (Hebbard and Ranscht 2014). Current evidence supports that adiponectin is a new risk factor for cancer and has a potential role as a diagnostic and prognostic biomarker (Dalamaga et al., 2012).

The ideal strategy for treating cancer cells is the down-regulation of adiponectin receptors in the early stages of cancer development, which would prevent

Table 3. The Relationship between the Clinicopathological Characteristics of Patients with Gastric Cancer and Survival

		n	Progression free survival(Mean±SE)	p value	Overall survival (Mean±SE)	p value
Age	<65	32	40.46 ±5.26	0.14	41.93±5.03	0.71
	65 years or older	25	44.75±8.34		44.87±8.18	
Sex	Female	18	46.50±9.14	0.28	47.14±9.04	0.33
	Male	39	36.18±4.82		37.49±4.62	
Location	Cardia	12	42.46±10.82	0.18	43.38±10.64	0.21
	Corpus	25	34.91 ±5.78		36.28±5.55	
	Antrum	20	47.16±8.40		47.46±8.38	
Tumor size	<5 cm	31	42.86± 5.78	0.45	43.44±5.69	0.46
	≥5 cm	26	34.59±7.02		36.06± 6.51	
Tumor stage	pT1+pT2	21	52.76+6.75	0.004	53.71±6.45	0.004
	pT3+pT4	36	28.78±4.17		29.60±4.05	
N stage	N0+N1	23	40.93±6.52	0.53	42.40±6.33	0.49
	N2+N3	34	37.15±5.69		37.48±5.54	
TNM	I+II	27	43.70±6.10	0.15	44.34±5.99	0.18
	III+IV	30	31.97±5.09		32.56±4.91	
Tumor type	Tubular	44	40.29±5.27	0.82	41.62±5.06	0.92
	Mucinous- signet ring	13	38.19±8.27		38.19±8.27	
Stage	Early	18	54.54±6.93	0.003	54.54±6.93	0.004
	Advanced	39	28.7±4.02		29.9±3.79	
Tumor differentiation	Well	11	55.14± 8.29	0.30	55.14±8.29	0.31
	Mild	22	38.33±8.16		39.71±7.77	
	Poor	24	32.22±5.98		32.42±5.83	
H. pylori	Not Exist	47	37.44±4.85	0.15	38.42±4.68	0.18
	Exist	10	50.37±10.5		51.15±10.4	
Perineural invasion	Not Exist	32	46.15± 5.66	0.05	46.24±5.62	0.07
	Exist	25	25.97±4.06		28.08±4.27	
Lymphatic invasion	Not Exist	33	43.30±5.38	0.53	44.18±5.17	0.47
	Exist	24	32.97±7.79		34.95±7.83	
Venovascular invasion	Not Exist	53	41.20±4.49	0.05	42.14±4.34	0.018
	Exist	4	9.37±1.85		9.37±1.85	
Adipo R1	Not Exist	48	40.89±4.66	0.83	41.57±4.61	0.97
	Exist	9	34.75±12.3		38.14±10.9	
Adipo R2	Not Exist	37	37.58±5.30	0.55	38.10±5.29	0.39
	Exist	20	44.78±8.12		46.17±7.45	

the antiproliferative effects of adiponectin. It has been proposed that AdipoR1/R2 expression is downregulated by gastric epithelial malignant transformation (Otani et al., 2010).

Ishikawa et al. proposed that low plasma adiponectin levels increase the risk for gastric cancer and play a role in its progression. They found that plasma adiponectin levels in gastric cancer were lower than those of a healthy control group. The plasma adiponectin level was also very low in upper gastric cancer (Ishikawa et al., 2005).

Moreover, adiponectin inhibits the proliferation of gastric cancer cell lines and peritoneal dissemination. It also has antineoplastic effects in gastric cancer. Adiponectin signals through Adipo-R1/R2 receptors (Ishikawa et al., 2007).

Seker et al. found that plasma adiponectin levels were higher in undifferentiated gastric tumors than in well-differentiated grade gastric tumors. However, they found no relationship between the patients' adiponectin levels and histopathological variables or demographic characteristics (Seker et al., 2010).

There are few immunohistochemical studies regarding Adipo-R1 and Adipo-R2 expression in patients with gastric cancer who underwent surgical resection (Barresi et al., 2009; Tsukada et al., 2011).

Increased adiponectin receptor expression was detected in breast (Körner et al., 2007), colorectal (Williams et al., 2008; Yoneda et al., 2008), pancreatic (Dalamaga et al., 2009), and esophageal (Ogunwobi and Beales 2008) carcinomas.

However, adiponectin receptor expression was lower in prostate cancer (Mistry et al., 2006; Michalakis et al., 2007). Baressi et al. reported that expression of adiponectin receptors 1 and 2 was significantly different in intestinal type gastric cancer patients and those with diffuse-type. Moreover, they found a statistically significant relationship between overall survival and Adipo-R1/R2 expression (Barresi et al., 2009; Tsukada et al., 2011).

Tsukada et al. found an inverse relationship between Adipo-R1 expression and tumor growth in gastric cancer. They proposed that Adipo-R1 expression can contribute significantly to the improvement of prognosis. However, they stated that Adipo-R2 expression has no effect on prognosis and has no relationship with clinicopathological factors (Tsukada et al., 2011).

Herein we investigate the relationship between the clinicopathological characteristics of cases with early and advanced stage gastric cancer with immunohistochemically-detected Adipo-R1 and Adipo-R2 expression based on pTNM stage. In addition, we conducted disease-free and overall survival analysis. In terms of histological grade, Adipo-R2 expression was significantly higher (p=0.011) in moderately differentiated tumors than in well-differentiated tumors. There was nearly a statistically significant relationship between TNM stage and Adipo-R2 expression (p=0.054). Adipo-R2 expression tends to be a little higher in cases with advanced stage gastric cancer. There is a strong relationship between *H. pylori* infection and gastric cancer (Karami et al., 2013). However, there was no significant relationship between *H. pylori* infection and Adipo-R1/R2 expression according to tumor stage. Further studies considering the many other factors involved in the pathogenesis of gastric cancer with larger sample sizes are necessary.

In conclusion, Adipo-R1 and Adipo-R2 are present in early and advanced stage gastric cancer. Unfortunately, there is no statistical difference with regards to survival.

Acknowledgements

This study was supported by the Scientific Research and Project Unit of Uludag University (Project number: UAP (T)-2010/36).

References

Arita Y, Kihara S, Ouchi N, et al (2002). Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation*, **105**, 2893-8.

Barresi V, Grosso M, Giuffre G, Tuccari G, Barresi G (2009). The expression of adiponectin receptors Adipo-R1 and Adipo-R2 is associated with an intestinal histotype and longer survival in gastric carcinoma. *J Clin Pathol*, **62**, 705-9.

Brakenhielm E, Veitonmäki N, Cao R, et al (2004). Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. *Proc Natl Acad Sci USA*, **101**, 2476-81.

Cnop M, Havel PJ, Utzschneider KM, et al (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*, **46**, 459-69.

Dalamaga M, Diakopoulos KN, Mantzoros CS (2012). The role of adiponectin in cancer: a review of current evidence. *Endocr Rev*, **33**, 547-94.

Dalamaga M, Migdalis I, Fargnoli JL, et al (2009). Pancreatic cancer express adiponectin receptors and is associated with hypoleptinemia and hyperadiponectemia: a case control study. *Cancer Causes Control*, **20**, 625-33.

Dal Maso L, Augustin LS, Karalis A, et al (2004). Circulating adiponectin and endometrial cancer risk. *J Clin Endocrinol Metab*, **89**, 1160-3.

Diez JJ, Iglesias P (2003). The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol*, **148**, 293-300.

Fenoglio-Preiser C, Carneiro F, Correa P, et al (2000). Gastric carcinoma. In: Hamilton SR, Aaltonen LA, eds. Tumours of the digestive system. Lyon: IARC Press, 39-52.

Gulcelik MA, Colakoglu K, Dincer H, et al (2012). Associations between adiponectin and two different cancers: breast and colon. *Asian Pac J Cancer Prev*, **13**, 395-8.

Hebbard L, Ranscht B (2014). Multifaceted roles of adiponectin in cancer. *Best Pract Res Clin Endocrinol Metab*, **28**, 59-69.

Ishikawa M, Kitayama J, Kazama S, et al (2005). Plasma adiponectin and gastric cancer. *Clin Cancer Res*, **11**, 466-72.

Ishikawa M, Kitayama J, Yamauchi T, et al (2007). Adiponectin inhibits the growth and peritoneal metastasis of gastric cancer through its specific membrane receptors AdipoR1 and AdipoR2. *Cancer Sci*, **98**, 1120-7.

Joshi RK, Lee SA (2014). Obesity related adipokines and colorectal cancer: a review and meta-analysis. *Asian Pac J Cancer Prev*, **15**, 397-405.

Kadowaki T, Yamauchi T (2005). Adiponectin and adiponectin receptors. *Endocr Rev*, **26**, 439-51.

Karami N, Talebkhan Y, Saberi S, et al (2013). Seroreactivity to *Helicobacter pylori* antigens as a risk indicator of gastric

cancer. *Asian Pac J Cancer Prev*, **14**, 1813-7.
Körner A, Pazaitou-Panayiotou K, Kelesidis T, et al (2007). Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. *J Clin Endocrinol Metab*, **92**, 1041-8.
Maeda K, Okubo K, Shimomura I, et al (1996). cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript1). *Biochem Biophys Res Commun*, **221**, 286-9.
Mantzoros C, Petridou E, Dessypris N, et al (2004). Adiponectin and breast cancer risk. *J Clin Endocrinol Metab*, **89**, 1102-7.
Michalakis K, Williams CJ, Mitsiades N, et al (2007). Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: a case control study. *Cancer Epidemiol Biomarkers Prev*, **16**, 308-13.
Mistry T, Digby JE, Chen J, Desai KM, Randeva HS (2006). The regulation of adiponectin receptors in human prostate cancer cell lines. *Biochem Biophys Res Commun*, **348**, 832-8.
Ogunwobi OO, Beales IL (2008). Globular adiponectin, acting via adiponcetin receptor-1, inhibits leptin-stimulated oesophageal adenocarcinoma cell proliferation. *Mol Cell Endocrinol*, **285**, 43-50.
Otani K, Kitayama J, Kamei T, et al (2010). Adiponectin receptors are downregulated in human gastric cancer. *Gastroenterol*, **45**, 918-27.
Petridou ET, Mitsiades N, Gialamas S, et al (2007). Circulating adiponectin levels and expression of adiponectin receptors in relation to lung cancer: two case-control studies. *Oncology*, **73**, 261-9.
Pinthus JH, Kleinmann N, Tisdale B, et al (2008). Lower plasma adiponectin levels are associated with larger tumor size and metastasis in clear-cell carcinoma of the kidney. *Eur Urol*, **54**, 866-73.
Seker M, Bilici A, Sonmez B, et al (2010). The association of serum adiponectin levels with histopathological variables in gastric cancer patients. *Med Oncol*, **27**, 1319-23.
Tsukada T, Fushida S, Harada S, et al (2011). Adiponectin receptor-1 expression is associated with good prognosis in gastric cancer. *J Exp Clin Cancer Res*, **30**, 107.
Williams CJ, Mitsiades N, Sozopoulos E, et al (2008). Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. *Endocr Relat Cancer*, **15**, 289-99.
Yamauchi T, Kamon J, Ito Y, et al (2003). Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*, **423**, 762-9.
Yokota T, Oritani K, Takahashi I, et al (2000). Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. *Blood*, **96**, 1723-32.
Yoneda K, Tomimoto A, Endo H, et al (2008). Expression of adiponectin receptors, AdipoR1 and AdipoR2, in normal colon epithelium and colon caner tissue. *Oncol Rep*, **20**, 479-83.