Cancer Causes Control (2009) 20:193–199
DOI 10.1007/s10552-008-9233-7

ORIGINAL PAPER

Low circulating adiponectin and resistin, but not leptin, levels are associated with multiple myeloma risk: a case–control study

Maria Dalamaga · Konstantinos Karmaniolas · Anna Panagiotou · Alex Hsi · John Chamberland · Cleanthi Dimas · Antigoni Lekka · Christos S. Mantzoros

Received: 26 December 2007 / Accepted: 18 August 2008 / Published online: 24 September 2008

Abstract Accumulating evidence supports a role for obesity in the etiology of multiple myeloma (MM). The distinct possibility exists that obesity may be linked to MM through altered adipokine secretion and circulating levels, one of which, adiponectin, has a protective role in several malignancies, including leukemia. In this case–control study, we investigated the role of serum adiponectin, resistin, and leptin levels in the etiopathogenesis of MM and we explored their association with several established prognostic factors. Seventy three patients with incident, histologically confirmed MM and 73 controls matched on gender and age were studied between 2001 and 2007, and blood samples were collected. Serum adiponectin, leptin, resistin, as well as MM prognostic parameters were determined. Statistical analysis of the data was performed using univariate and multivariate analyses. Lower serum adiponectin and resistin levels were associated with higher risk of MM by bivariate analysis and after adjusting for age, gender, BMI, and serum levels of leptin ($p < 0.0001$). Adiponectin may have a protective role in MM, whereas leptin was not associated with risk for MM at a comparable level of significance and resistin levels may be decreased via a compensatory mechanism. Further studies are needed to confirm these associations and to explore the mechanisms underlying adiponectin's role in MM and plasma cell dyscrasias.

Keywords Adiponectin · Leptin · Resistin · Adipokine · Multiple myeloma

M. Dalamaga · A. Panagiotou · C. Dimas
Department of Clinical Biochemistry, Medical School, University of Athens, "Attikon", General University Hospital, 1 Rimini Street, Chaidari, 10024 Athens, Greece

M. Dalamaga · A. Lekka
Department of Laboratory Hematology, NIMTS General Hospital, 12 Monis Petraki, and Vas.Sofias Avenue, 11521 Athens, Greece

K. Karmaniolas
Department of Internal Medicine-Hematology Section, NIMTS General Hospital, 12 Monis Petraki and Vas.Sofias Avenue, 11521 Athens, Greece

A. Hsi · J. Chamberland · C. S. Mantzoros (✉)
Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, ST816, Boston, MA 02215, USA
e-mail: cmantzor@bidmc.harvard.edu

Introduction

Multiple myeloma (MM), a neoplasm of mature and immature plasma cells resulting in an overproduction of heavy and light chain monoclonal immunoglobulins [1, 2], accounts for approximately 0.8% of all cancer diagnoses and 0.9% of cancer deaths [3]. MM incidence rates are higher in older subjects, among males than females, and highest amid African Americans [1, 4], but the etiology of MM remains largely unknown with no established risk factors other than senescence, male gender, African American ethnicity, monoclonal gammopathy of undetermined significance (MGUS), and positive family history of lymphohematopoietic cancer [2, 5]. Several potential etiologic factors including exposure to chemicals and radiation have been suggested but findings remain inconsistent [5, 6]. Chronic immune stimulation has also been implicated as a risk factor in several but not all studies [4–7], whereas accumulating evidence supports a role for obesity in the etiology of MM [5, 8–11].

The adipose tissue is currently considered an active endocrine organ participating in the modulation of insulin sensitivity and resistance, energy homeostasis, bone metabolism, inflammation, hematopoiesis, immunity, and angiogenesis [12–14]. The adipose tissue secretes a number of proinflammatory and anti-inflammatory adipokines, such as adiponectin and leptin as well as cytokines and chemokines, including TNF-α and IL-6 [15]. Adiponectin, an endogenous insulin sensitizer, has been found to play a protective role for several types of malignancies in vivo, notably, those related to obesity including leukemia [16–23]. Resistin, a novel hormone secreted by adipocytes and mononuclear cells, was discovered as a hormone related to insulin resistance, but studies in mice have revealed conflicting data and more recent studies in humans have suggested that the physiologic role of resistin is mainly related to inflammation [24].

Thus, the distinct possibility exists that obesity may be linked to MM through altered secretion of one of these adipokines. Two previous studies with small number of cases have examined leptin in association with MM [25, 26]. No previous study has focused on adiponectin or resistin as predictors of MM and no prior study has explored simultaneously whether adiponectin, leptin, and/or resistin are associated with MM. In this case–control study, we investigate the role of adiponectin, leptin, and resistin levels, individually and jointly, in the etiopathogenesis of MM and explore their association with several prognostic factors.

Materials and methods

In this study, cases and controls were recruited from patients hospitalized at the Veterans' Administration General Hospital of Athens (NIMTS). This hospital is the only Veteran's Hospital in the Athens Metropolitan area and the entire Southern Greece. The study included 73 cases and 73 controls under the age of 79 years from the same study base, who were all of Greek nationality and permanent residents of Greece. Medical records were reviewed and interviews were carried out to obtain information on demographic characteristics, medical history, as well as weight and height.

Selection of cases

Eligible cases included newly diagnosed patients under age 79 with histologically confirmed multiple myeloma according to the cytologic, clinical, and laboratory diagnostic criteria of Durie and Salmon [27], consecutively admitted to the Internal Medicine Department-Hematology Section of the Veterans' Hospital between 18 January 2001 and 25 August 2007. A total of 77 cases were identified, and of those, 73 cases (42 males and 31 females), aged 55 to 79 years (median age, 68) consented to participate and were interviewed. The main reasons for nonparticipation were the status of the patient and/or refusal on the part of the subject or his/hers relatives. Nevertheless, responders and non-responders did not differ on demographic variables, notably, age, gender, and time of diagnosis.

Selection of controls

Controls were patients, under age 79, admitted for non-neoplastic and non-infectious conditions to the Opthalmologic and Orthopedic Department of the same hospital and matched to cases on age (±5 years), gender, and year/month of diagnosis (±1 month). No control developed MM. The main causes of admission to the hospital in the control group were: scheduled senile cataract operation (43.8%), scheduled hip (20.5%) or knee joint replacement (19.2%) due to idiopathic osteoarthritis and injuries, in particular fractures not secondary to a disease (16.4%). For every eligible case, an attempt was made to randomly identify a control admitted to the Veterans' Administration General Hospital as closely as possible in time to the admission of the corresponding case (±1 month). A total of 95 potential controls were identified, and of those, 73 consented to participate and were interviewed. Among the latter, 42 were male and 31 female, aged 53 to 79 years (median age, 68). As for cases, the main reason for non participation was the status of the patient and/or refusal on the part of the subject or his/her relatives, but responders and non-responders did not differ on demographic variables, notably, age, gender, and time of diagnosis. All cases and controls who participated in our investigation were fully informed of the aim of the study and gave written consent for their participation and their agreement that the results of this study may well be presented or published, solely in the interests of science, provided that their anonymity is maintained.

Diagnostic procedures, specimen collection, and laboratory analysis

The diagnosis of multiple myeloma was made according to standard clinical and laboratory diagnostic procedures according to the criteria of Durie and Salmon [27]. Serum lactic dehydrogenase (LDH), calcium, C-reactive protein (CRP), β_2-microglobulin, as well as erythrocyte sedimentation rate (ESR) were determined. Multiple myeloma patients were also classified in three prognostic stages using the Durie-Salmon Myeloma Staging System [28]. All blood specimens were collected prior to the initiation of

chemotherapy or blood transfusions for the cases and prior to any therapeutic approach, including surgery, for the control group. Peripheral blood samples were centrifuged in the laboratory. Serum was separated and stored at −80°C. Samples from cases and controls were handled in a similar way concerning the amount of time between collection, processing, and initial storage, as well as the amount of time in storage prior to hormones assays performance. Assays were run blindly and the laboratory technicians were not aware of the study hypothesis and the case/control status of the patients. Serum leptin and adiponectin levels were measured using ELISA (Avibion Human Elisa, Orgenium Laboratories, Helsinki, Finland). The sensitivity of the assay was 1 ng/ml and 3 ng/ml for leptin and adiponectin, respectively. The intra-assay coefficient of variation was <9% and <10% for leptin and adiponectin, respectively, while the inter-assay coefficient of variation was <12% for adiponectin and leptin. Serum resistin was determined using ELISA (Phoenix Pharmaceuticals, Inc, Burlingame, CA 94010, US). The sensitivity of the assay was 0.016 ng/ml. The intra-assay coefficient of variation was <10%, while the inter-assay coefficient of variation was <15%.

Statistical analysis

Descriptive characteristics of multiple myeloma case and control subjects are presented as proportions or as mean values ± standard deviation (SD). Comparisons between cases and controls was conducted by using chi-square tests for categorical variables and *t*-test for continuous variables. Nonparametric Spearman correlation test were conducted to examine the associations of hormones and metabolic characteristics. Subsequently, statistical analysis was undertaken through multiple logistic regression using both conditional and unconditional analysis. Results were very similar with respect to effect size and precision for conditional and unconditional analysis; thus, we have opted for presenting herein unconditional rather than conditional analysis using the same approach when investigating prognostic stages of multiple myeloma.

In the case–control analyses, samples were stratified by control-based quartile of adiponectin, leptin, and resistin to test the associations of each hormone with MM. Each model used simple and multivariate unconditional logistic regression to produce crude and adjusted risk estimates. For simple *t*-tests, statistical significance was set at 0.017 to adjust for multiple comparisons (three hormones of interest). One-way ANOVA with Bonferroni correction was conducted to compare cases among the different subgroups of multiple myeloma characteristics. Statistical analysis of the data was performed with SAS 9.1 for Windows XP (SAS Institute, Cary, N.C.) [29].

Results

Cases and controls were matched by gender, age (within five years), and date of diagnosis (within one month). Cases had significantly higher weight, BMI, and levels of serologic prognostic parameters of MM than control subjects. Adiponectin and resistin levels of control subjects were significantly higher than levels of case subjects, but leptin levels of controls were significantly lower than that of cases (Table 1). Leptin was positively associated with CRP, LDH, and calcium, and negatively correlated with adiponectin. Further adjusting for both BMI, age, and gender did not alter the associations (data not shown).

Table 2 displays the odd ratios for multiple myeloma in relation to adiponectin, leptin, and resistin levels by control-based quartiles. In unadjusted analyses, higher levels of adiponectin and resistin were found to be associated with significantly lower risk for multiple myeloma. Adjusting for age, gender, date of diagnosis, BMI, and other adipokines did not alter the reported associations and significance levels (Table 2A, C). In contrast to adiponectin and resistin, leptin showed no significant association with risk for multiple myeloma (Table 2B). It is important to highlight that the odds ratios (OR) for the highest quartile of leptin levels were quite strong despite they

Table 1 Descriptive characteristics of subjects with multiple myeloma (n = 73) and controls (n = 73)

	Cases	Controls	p Value
n	73	73	
Male, n/Female, n	31/42	31/42	1.0
Age, years, mean (SD)	67.1 (5.9)	68.0 (5.8)	0.34
Weight, kg, mean(SD)	78.9 (12.3)	74.6 (13.0)	0.04
Height, m, mean(SD)	1.69 (0.07)	1.69 (0.08)	0.90
BMI, mean(SD)	27.7 (4.0)	26.2 (4.2)	0.03
WHO categories of BMI, n(%)			
Normal (18.5–25)	21 (28.8)	34 (46.6)	0.03
Overweight (25–30)	34 (46.6)	25 (34.2)	0.13
Obese (30–35)	13 (17.8)	10 (13.7)	0.50
Clinically obese (35–40)	5 (6.8)	4 (5.5)	0.73
Leptin, ng/ml, mean(SD)	27.5 (17.6)	21.9 (9.5)	0.02
Resistin, ng/ml, mean(SD)	9.4 (5.0)	15.9 (6.8)	<0.0001
Adiponectin, ng/ml, mean(SD)	14.3 (7.3)	21.7 (10.3)	<0.0001
Stage, n(%)			
I	15 (20.5)		
II	28 (38.4)		
III	30 (41.1)		
Paraprotein, n(%)			
IgG class	40 (54.8)		
IgA class	21 (28.8)		
Light chain class	12 (16.4)		

being non-significant. The inability to detect a cleaner trend across leptin quartiles may reflect underlying biology and/or be a function of the small sample size and the relatively small differences in absolute levels captured in the lower three quartiles. In conditional logistic regression models, the crude ORs (95% CI) across quartiles of adiponectin were as follows: 0.46 (0.18–1.19) for Q2, 0.14 (0.04–0.54) for Q3, and 0.04 (0.01–0.22) for Q4 ($p = 0.002$). Crude ORs (95% CI) from conditional logistic regression across quartiles of leptin were 1.55 (0.63–3.82) for Q2, 1.02 (0.39–2.67) for Q3, and 2.58 (0.96–6.95) for Q4 ($p = 0.22$). The crude ORs (95% CI) from conditional logistic regression across quartiles of resistin were 0.42 (0.16–1.12) for Q2, 0.11 (0.03–0.43) for Q3, and 0.03 (0.01–0.20) for Q4 ($p = 0.001$). Since conditional and unconditional logistic regression models produced nearly identical results with respect to effect size and precision, only the results from the unconditional logistic regression are presented in Table 2.

Table 3 displays the associations of adipokines with multiple myeloma stages and paraprotein types among cases. Leptin levels were significantly different among multiple myeloma stages. Higher stages tended to present higher levels of leptin (Table 3). The differences in mean leptin levels by stage were not small, especially those between stages II and III. Adjustment for age, gender, and BMI didn't alter substantially the difference of mean leptin levels ($p < 0.02$ vs. a Bonferonni adjusted p value of

Table 2 Odd ratios and 95% CI for risk of multiple myeloma by control defined quartiles of adiponectin (A), leptin (B), and resistin (C)[a]

A	Quartile of adiponectin				*p* Value
	Q1	Q2	Q3	Q4	
Cases (*n*)/Controls (*n*)	40/19	19/18	11/18	3/18	
Adiponectin (range), μg/ml	(2.3–14.8)	(14.8–19.8)	(19.8–27.8)	(27.8–49.2)	
Median, μg/ml	10.2	17.5	23.7	32.2	
Cases vs. control subjects					
Crude	1.0	0.50 (0.22–1.17)	0.29 (0.12–0.73)	0.08 (0.02–0.30)	0.0007
Age, Gender, date of diagnosis, and BMI adjusted	1.0	0.44 (0.18–1.07)	0.25 (0.09–0.68)	0.06 (0.01–0.25)	<0.001
Age, Gender, date of diagnosis, BMI, leptin, and resistin adjusted	1.0	0.72 (0.23–2.29)	0.27 (0.08–0.95)	0.08 0.02–0.42)	0.001
B	Quartile of leptin				*p* Value
	Q1	Q2	Q3	Q4	
Cases (*n*)/Controls (*n*)	13/18	19/18	13/18	28/19	
Leptin (range), ng/ml	(3.9–15.2)	(15.2–22.4)	(22.4–26.9)	(26.9–96.7)	
Median, μg/ml	11.3	18.9	24.8	33.0	
Cases vs. control subjects					
Crude	1.0	1.46 (0.56–3.82)	0.92 (0.33–2.56)	2.11 (0.84–5.30)	0.25
Age, Gender, date of diagnosis, and BMI adjusted	1.0	1.65 (0.59–4.44)	0.99 (0.35–2.86)	2.09 (0.79–5.52)	0.24
Age, Gender, date of diagnosis, BMI, adiponectin, and resistin adjusted	1.0	1.53 (0.39–6.01)	0.83 (0.21–3.28)	2.71 (0.77–9.57)	0.18
C	Quartile of resistin				*p* Value
	Q1	Q2	Q3	Q4	
Cases (*n*)/Controls (*n*)	43/19	19/18	9/18	2/18	
Resistin (range), ng/ml	(1.2–11.0)	(11.0–13.9)	(13.9–19.5)	(19.5–32.9)	
Median, μg/ml	7.4	12.8	16.9	24.7	
Cases vs. control subjects					
Crude	1.0	0.47 (0.20–1.08)	0.22 (0.08–0.58)	0.05 (0.01–0.23)	0.0002
Age, gender, date of diagnosis, and BMI adjusted	1.0	0.30 (0.11–0.80)	0.13 (0.04–0.39)	0.03 (0.01–0.18)	0.0001
Age, gender, date of diagnosis BMI, leptin, and adiponectin adjusted	1.0	0.26 (0.09–0.79)	0.08 (0.02–0.31)	0.03 (0.004–0.17)	<0.0001

[a] Cases and controls are matched on age, gender, and date of diagnosis

0.017). No significantly different adiponectin or resistin levels were found among different prognostic stages and paraprotein classes.

Discussion

This case–control study provides evidence that higher serum adiponectin and resistin levels are associated with lower risk of MM before and after controlling for age, gender, BMI, and serum levels of adipokines. Several epidemiologic studies have shown inverse associations between adiponectin levels and risk for breast [16], endometrial [17], prostate [18], gastric [19], renal [20], colorectal [21] cancers, as well as melanoma [22] and childhood leukemia (AML) [23]. Adiponectin, the product of the apM1 gene, is specifically expressed in human white tissue adipocytes and is inversely related to the degree of adiposity [15]. Adiponectin may act as an anti-inflammatory hormone by suppressing the activation of the nuclear transcription factor κB and thus inhibiting cytokine secretion by adipocytes and other immune cells, including interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) [30–32]. Several cytokines contribute to the growth of myeloma cells and MM pathogenesis, but the most important appears to be IL-6 [1, 30]. IL-6 production and action are regulated by endocrine, autocrine, and paracrine mechanisms [30]. Reduced adiponectin levels observed in MM could be responsible in part for IL-6 and TNF-α overproduction in the bone marrow milieu. Although adiponectin was a significant predictor for MM risk, we haven't been able to find either a significant association between adiponectin levels and MM prognostic stages or a significant relation between adiponectin levels and prognostic biological parameters such as CRP [1, 30],

We have also found that MM patients tend to have higher mean leptin levels than controls by univariate analysis, which may reflect their higher degree of obesity. This is in agreement with two previous studies examining much fewer patients (14 and 62 patients) [25, 26]. We also report herein that after adjusting for age, gender, and BMI, as well as for multiple comparisons performed, serum leptin levels weren't significantly different between MM patients and controls. The odds of having a highest-quartile leptin level were close to three times as high among cases than among controls, but the OR was unstable and not statistically significant. Leptin, a 16-kd protein encoded by the *obese* gene, is mainly secreted by white adipocytes and is positively correlated with body fat mass [14]. Leptin receptor (OB-Rb), which shows homologies to cytokine and hematopoietic growth factor receptors, is expressed in all cell types of innate and adaptive immunity [13]. Whether, as previously proposed, leptin (circulating or produced by bone marrow adipocytes and stromal cells) and its receptor OB-R may function as a growth factor/receptor-ligand system in malignant plasma cells acting in a paracrine fashion remains to be demonstrated. Although leptin regulates T-cell proliferation and influences cytokine production from T-cells and monocytes [12, 14], and leptin may stimulate leukemic cell growth in vitro [13, 33], leptin's action in humans in vivo is restricted mainly in leptin deficient states [12, 14, 34]. Thus, currently available evidence indicates that leptin has only a permissive role in humans [12, 14, 34], a notion consistent with our data presented herein.

Resistin, an adipokine that belongs to the family of resistin-like molecules (RELMs) was originally discovered as a molecule that reportedly induced insulin resistance or impaired hepatic sensitivity to insulin and caused hyperglycemia without affecting peripheral insulin sensitivity [35, 36]. Furthermore, resistin may upregulate several adhesion molecules and cytokines [37]. However, data in humans are controversial. In contrast to mice, resistin in humans is expressed in lower levels in adipocytes but at relatively higher levels in circulating blood monocytes [38]. Several studies have failed to detect increased serum resistin levels in obese or insulin resistant subjects [24]. Currently, resistin is viewed mainly as an inflammatory factor associated with TNF-α, IL-6, and CRP [39]. However, MM patients in this study, resistin levels were lower; given the proposed biological roles for resistin, this finding could be possibly due to a compensatory response of the resistin pathway to the upregulation of other inflammatory and proliferative factors, which may be etiologically linked to MM. Thus, low resistin levels could be associated with upregulation of other adipo- or cytokines etiologically involved in MM and could in turn be decreased in a compensatory way, which would ultimately lead to a less inflammatory state.

The slightly higher BMI observed among cases than controls is roughly consistent with previously reported positive association of obesity with MM risk [11]. Although previous studies have implicated obesity in MM risk [8–10], the potential mechanisms by which obesity may augment MM risk have to be fully elucidated. Proposed mechanisms include an increased total number of plasma cells that could undergo malignant transformation and the contribution of cytokines involved in the proliferation and survival of plasma cells [30]. Other endocrine factors could play an important role in plasma cell transformation, including factors associated with insulin resistance such as insulin-like growth hormone, which can stimulate proliferation and inhibit apoptosis in myeloma cells [8]. Adiponectin is a hormone with insulin sensitizing and anti-inflammatory properties, whereas resistin has been linked with opposite functions.

This is the first study exploring simultaneously the role of adiponectin, leptin, and resistin in MM. We included

Table 3 Associations of leptin, adiponectin, and resistin with multiple myeloma stages and paraprotein classes before (A) and after adjusting for age, gender, date of diagnosis, and BMI (B)

	Leptin		Adiponectin		Resistin	
	Mean (SE)	*p* Value	Mean (SE)	*p* Value	Mean (SE)	*p* Value
A						
Stage		0.01		0.83		0.94
I	20.8 (4.3)		15.2 (1.9)		9.4 (1.3)	
II	23.3 (3.2)		13.8 (1.4)		9.2 (1.0)	
III	34.7 (3.1)		14.2 (1.3)		9.6 (0.9)	
Paraprotein		0.26		0.88		0.56
IgG class	22.1 (3.8)		13.6 (1.6)		9.7 (1.1)	
IgA class	29.5 (2.8)		14.5 (1.2)		9.7 (0.8)	
Light chain class	30.1 (5.1)		14.7 (2.1)		8.0 (1.5)	
B						
Stage		0.02		0.53		0.82
I	21.0 (4.5)		16.1 (2.0)		8.7 (1.4)	
II	23.6 (3.2)		13.3 (1.4)		9.5 (1.0)	
III	34.4 (3.0)		14.2 (1.3)		9.7 (0.9)	
Paraprotein		0.34		0.87		0.69
IgG class	22.8 (3.8)		13.6 (1.6)		9.5 (1.1)	
IgA class	29.1 (2.7)		14.6 (1.2)		9.7 (0.8)	
Light chain class	30.4 (5.0)		14.2 (2.1)		8.3 (1.5)	

hospital controls with admission diagnoses not known to be related with the principal exposure variables, i.e., adiponectin, leptin, and resistin, as well as obesity. Neither the study subjects nor laboratory personnel were aware of the study hypotheses, a fact that eliminates bias from these sources. Assays were run blindly minimizing error from that source too. Random misclassification is possible but this would have been expected to depress effect estimates toward the null and thus could not account for the significant results reported herein. An important limitation of the present study is its cross-sectional nature, whereas causality cannot be inferred. Adipokine levels may in part reflect a physiologic consequence of multiple myeloma presence rather than an etiologic effect. The rarity of MM in the general population makes the case–control study design more appropriate for studying adipokines in its etiopathogenesis than a cohort study design. Despite its small size, this case–control study was of size similar to prior studies on adiponectin in other malignancies and, in addition, was adequate to generate statistically significant associations with adipokines.

In summary, the results of our study provide support to the hypothesis that adiponectin may have a protective role in MM, whereas leptin, a reflection of the degree of obesity, is not independently associated with risk for MM and resistin levels may be decreased via a compensatory mechanism. The hypothesis raised herein and the mechanisms underlying adiponectin's role in MM and plasma cell dyscrasias require further investigation.

Acknowledgment This study was supported by a discretionary grant from BIDMC.

References

1. Foerster J, Paraskevas F (1998) Multiple myeloma. In: Lee GR, Foerster J, Luken J, Paraskevas F, Greer JP, Rodgers GM, Wintrobe MM (eds) Wintrobe's clinical hematology, vol 2. Lippincott Williams & Wilkins, Baltimore, pp 2631–2655
2. Kyle RA, Rajkumar SV (2004) Multiple myeloma. N Engl J Med 351:1860–1873. doi:10.1056/NEJMra041875
3. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
4. Lewis DR, Pottern LM, Brown LM, Silverman DT, Hayes RB, Schoenberg JB, Greenberg RS, Swanson GM, Schwartz AG, Liff JM (1994) Multiple myeloma among blacks and whites in the United States: the role of chronic antigenic stimulation. Cancer Causes Control 5:529–539. doi:10.1007/BF01831381
5. Alexander DD, Mink PJ, Adami HO, Cole P, Mandel JS, Oken MM, Trichopoulos D (2007) Multiple myeloma: a review of the epidemiologic literature. Int J Cancer 120:40–61. doi:10.1002/ijc.22718
6. Morgan GJ, Davies FE, Linet M (2002) Myeloma aetiology and epidemiology. Biomed Pharmacother 56:223–234. doi:10.1016/S0753-3322(02)00194-4
7. Bourguet CC, Logue EE (1993) Antigenic stimulation and multiple myeloma. A prospective study. Cancer 72:2148–2154. doi :10.1002/1097-0142(19931001)72:7<2148::AID-CNCR2820720714>3.0.CO;2-Q
8. Blair CK, Cerhan JR, Folsom AR, Ross JA (2005) Anthropometric characteristics and risk of multiple myeloma. Epidemiology 16:691–694. doi:10.1097/01.ede.0000172135.61188.2d
9. Birmann BM, Giovanucci E, Rosner B, Andesrson KC, Colditz GA (2007) Body mass index, physical activity and risk of

multiple myeloma. Cancer Epidemiol Biomarkers Prev 16:1474–1478. doi:10.1158/1055-9965.EPI-07-0143
10. Chiu BC, Gapstur SM, Greenland P, Wang R, Dyer A (2006) Body mass index, abnormal glucose metabolism and mortality from hematopoietic cancer. Cancer Epidemiol Biomarkers Prev 15:2348–2354. doi:10.1158/1055-9965.EPI-06-0007
11. Larsson SC, Wolk A (2007) Body mass index and risk of multiple myeloma: a meta-analysis. Int J Cancer 121:2512–2516. doi:10.1002/ijc.22968
12. Chan JL, Moschos SJ, Bullen J, Heist K, Li X, Kim YB, Kahn BB, Mantzoros CS (2005) Recombinant methionyl human leptin administration activates signal transducer and activator of transcription 3 signaling in peripheral blood mononuclear cells in vivo and regulates soluble tumor necrosis factor-alpha receptor levels in humans with relative leptin deficiency. J Clin Endocrinol Metab 90:1625–1631. doi:10.1210/jc.2004-1823
13. Matarese G, Moschos S, Mantzoros CS (2005) Leptin in immunology. J Immunol 174:3137–3142
14. Brennan AM, Mantzoros CS (2006) Drug Insight: the role of leptin in human physiology and pathophysiology-emerging clinical applications. Nat Clin Pract Endocrinol Metab 2:318–327. doi:10.1038/ncpendmet0196
15. Kershaw EE, Flier JS (2004) Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 89:2548–2556. doi:10.1210/jc.2004-0395
16. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, Papadiamantis Y, Markopoulos C, Spanos E, Chrousos G, Trichopoulos D (2004) Adiponectin and breast cancer risk. J Clin Endocrinol Metab 89:1102–1107. doi:10.1210/jc.2003-031804
17. Dal Maso L, Augustin LS, Karalis A, Talamini R, Franceschi S, Trichopoulos D, Mantzoros CS, La Vecchia C (2004) Circulating adiponectin and endometrial cancer risk. J Clin Endocrinol Metab 89:1160–1163. doi:10.1210/jc.2003-031716
18. Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, Bedir S (2005) Prostate cancer and adiponectin. Urology 65:1168–1172. doi:10.1016/j.urology.2004.12.053
19. Ishikawa M, Kitayama J, Kazama S, Hiramatsu T, Hatano K, Nagawa H (2005) Plasma adiponectin and gastric cancer. Clin Cancer Res 11:466–472. doi:10.1158/1078-0432.CCR-04-1453
20. Spyridopoulos TN, Petridou ET, Skalkidou A, Dessypris N, Chrousos GP, Mantzoros CS (2007) Low adiponectin levels are associated with renal cell carcinoma: a case–control study. Int J Cancer 120:1573–1578. doi:10.1002/ijc.22526
21. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS (2005) Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. J Natl Cancer Inst 97:1688–1694
22. Mantzoros CS, Trakatelli M, Gogas H, Dessypris N, Stratigos A, Chrousos GP, Petridou ET (2007) Circulating adiponectin levels in relation to melanoma: a case–control study. Eur J Cancer 43:1430–1436. doi:10.1016/j.ejca.2007.03.026
23. Petridou E, Mantzoros CS, Dessypris N, Dikalioti SK, Trichopoulos D (2006) Adiponectin in relation to childhood myeloblastic leukaemia. Br J Cancer 94:156–160. doi:10.1038/sj.bjc.6602896
24. Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, Orlova C, Mantzoros CS (2003) Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab 88:4848–4856. doi:10.1210/jc.2003-030519
25. Pamuk GE, Demir M, Harmandar F, Yesil Y, Turgut B, Vural O (2006) Leptin and resistin levels in serum of patients with hematologic malignancies: correlation with clinical characteristics. Exp Oncol 28:241–244
26. Alexandrakis MG, Passam FH, Sfiridaki A, Pappa CA, Moschandrea JA, Kandidakis E, Tsirakis G, Kyriakou DS (2004) Serum levels of leptin in multiple myeloma patients and its relation to angiogenic and inflammatory cytokines. Int J Biol Markers 19:52–57
27. Durie BGM (1986) Staging and kinetics of multiple myeloma. Semin Oncol 13:300–309
28. Durie BGM, Salmon SE (1975) A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. Cancer 36:842–854. doi :10.1002/1097-0142(197509)36:3<842::AID-CNCR2820360303>3.0.CO;2-U
29. SAS/STAT User's Guide (1989) NC, Cary. Ref Type: Computer Program
30. Lauta VM (2003) A review of the cytokine network in multiple myeloma: diagnostic, prognostic and therapeutic implications. Cancer 97:2440–2452. doi:10.1002/cncr.11072
31. Ajuwon KM, Spurlock ME (2005) Adiponectin inhibits LPS-induced NF-kB activation and IL-6 production and increases PPARγ2 expression in adipocytes. Am J Physiol Regul Integr Comp Physiol 288:1220–1225. doi:10.1152/ajpregu.00397.2004
32. Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME (2004) Adiponectin differentially regulates cytokines in porcine macrophages. Biochem Biophys Res Commun 316:924–929. doi:10.1016/j.bbrc.2004.02.130
33. Nakao T, Hino M, Yamane T, Nishizawa Y, Morii H, Tatsumi N (1998) Expression of the leptin receptor in human leukaemic blast cells. Br J Haematol 102:740–745. doi:10.1046/j.1365-2141.1998.00843.x
34. Chan JL, Matarese G, Shetty GK, Raciti P, Kelesidis I, Aufiero D, De Rosa V, Perna F, Fontana S, Mantzoros CS (2006) Differential regulation of metabolic, neuroendocrine, and immune function by leptin in humans. Proc Natl Acad Sci USA 103:8481–8486. doi:10.1073/pnas.0505429103
35. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA (2001) The hormone resistin links obesity to diabetes. Nature 409:307–312. doi:10.1038/35053000
36. Rajala MW, Obici S, Scherer PE, Rossetti L (2003) Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. J Clin Invest 111:225–230
37. Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, Manabe I, Utsunomiya K, Nagai R (2004) Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun 314:415–419. doi:10.1016/j.bbrc.2003.12.104
38. Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, O'Rahilly S (2001) Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. Diabetes 50:2199–2202. doi:10.2337/diabetes.50.10.2199
39. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ (2005) Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 111:932–939. doi:10.1161/01.CIR.0000155620.10387.43