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Prediagnostic Plasma Adiponectin and Survival among Patients with Colorectal Cancer

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Abstract

Circulating adiponectin is inversely related to the risk of colorectal cancer (CRC). However, its influence on CRC survival is unclear. We conducted a prospective study to evaluate the association between prediagnostic plasma levels of adiponectin and mortality in patients with CRC. We identified 621 incident CRC cases who provided blood specimens prior to diagnosis within the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). After a median follow-up of 9 years, there were 269 (43%) total deaths, of which 181 (67%) were due to CRC. Compared with participants in the lowest quartile of adiponectin, those in the highest quartile had multivariate HRs of 1.89 (95% CI, 1.21–2.97; P_{trend} = 0.01) for CRC-specific mortality and 1.66 (95% CI, 1.15–2.39; P_{trend} = 0.009) for overall mortality. The apparent increased risk in CRC-specific mortality was more pronounced in patients with metastatic disease (HR 3.02, 95% CI, 1.50–6.08). Among patients with CRC, prediagnostic

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plasma adiponectin is associated with an increased risk of CRC-specific and overall mortality, and is more apparent in patients with metastatic disease. Adiponectin may be a marker for cancers which develop through specific pathways that may be associated with worsened prognosis. Further studies are needed to validate these findings.

Keywords

Adiponectin; survival; colorectal cancer

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer-related deaths in the United States (1). Obesity is a well-established risk factor for CRC (2, 3). Furthermore, prediagnostic obesity has been associated with worsened survival among patients with CRC (4, 5). However, the underlying mechanism by which obesity influences the development of CRC or outcomes after CRC diagnosis is unclear. Several mechanisms have been hypothesized, including alteration of the adipokine milieu, perturbations of the insulin growth factor 1 (IGF1) axis, and chronic low-grade inflammation (6, 7).

Adipose tissue is the largest endocrine organ responsible for the regulation of inflammation and metabolism, and the synthesis of cytokines and hormones (8). The most abundant hormone secreted by adipose tissue is adiponectin, a 30-kDA protein hormone that exists as low molecular weight (LMW) and high molecular weight (HMW) multimers in the circulation (9). Its multitude of metabolic functions is effected by binding primarily to adiponectin receptor 1 (ADIPOR1) that is found in skeletal muscle and adiponectin receptor 2 (ADIPOR2) that resides in hepatocytes (10). Accumulating evidence supports an inverse relationship between circulating adiponectin and obesity, suggesting the possibility that adiponectin may mediate the biological link between obesity and CRC (11, 12). In addition, higher levels of expression of adiponectin receptors are observed in CRC compared to normal tissues, further supporting this hypothesis (13).

To date, adiponectin's pleiotropic roles in carcinogenesis are complex and remain controversial. Its anti-carcinogenic properties have been attributed to the activation of adenosine monophosphate-activated protein kinase (AMPK; PRKAA) pathway, leading to apoptosis and anti-proliferation (14), direct inhibition of the phosphoinositide 3-kinase (PI3K)/protein kinase-B (AKT) pathway which is responsible for cell survival (15), and modulation of insulin sensitization (16) and inflammation (17). In contrast, adiponectin has been shown to propagate oncogenesis through stimulation of pro-inflammatory cytokines such as interleukin (IL)-8 (18), inhibition of apoptosis via activation of AMPK/Sirtulin 1 (SIRT1)/PPAR gamma coactivator 1-alpha (PGC-1α) (19), and promotion of angiogenesis (20, 21) and colonic proliferation (18).

Several epidemiological studies have established an inverse correlation between circulating adiponectin and the incidence of CRC (22–25). Among 616 incident CRC cases and 1,205 controls within the Nurses' Health Study (NHS) and Health Professionals Follow-up Study

(HPFS), we have reported that plasma adiponectin was significantly associated with a lower risk of CRC among men [relative risk (RR) 0.55, 95% CI, 0.35–0.86; P_{trend} = 0.02], but not women (RR 0.96, 95% CI, 0.67–1.39; P_{trend} = 0.74) (25). In contrast, there is a paucity of data on adiponectin's impact on survival among patients with established CRC. The only prospective study showed that adiponectin (measured at time of diagnosis) was not predictive of CRC survival (26). Another recent study reported that adiponectin (measured at time of diagnosis) conferred a worse prognosis in patients with hepatocellular carcinoma (HCC) (27). Hence, we prospectively assessed the influence of prediagnostic plasma adiponectin on mortality in patients with CRC.

Materials and Methods

Study Population

Our study comprised of 621 incident CRC cases within the NHS and the HPFS cohorts. The NHS began in 1976 and enrolled 121,700 US female registered nurses, aged 30 – 55 years. The HPFS began in 1986 and enrolled 51,529 male health professionals (podiatrists, dentists, osteopathic physicians, veterinarians, pharmacists, and optometrists), aged 40–75 years. Biennially, follow-up questionnaires were administered to collect information with respect to lifestyle factors such as smoking, physical activity, body weight, family history of CRC, use of aspirin and non-steroidal anti-inflammatory drug (NSAIDs), endoscopic screening, and medical history. Dietary information was updated every four years using validated food frequency questionnaires (FFQ) (28, 29). High follow-up rates were appreciated for both cohorts, 95.4% in NHS and 95.9% in HPFS. The Institutional Review Board at the Brigham and Women's Hospital and the Harvard School of Public Health approved the study. The completion of self-administered questionnaires by participants were considered to imply informed consent.

Exposure Assessment

Phlebotomy kits were mailed to all the participants. 32,826 NHS participants and 18,225 HPFS participants returned blood samples on ice packs by overnight courier from 1989 to 1990 and 1993 to 1995 respectively. Upon receipt of the blood samples in the laboratory, they were immediately centrifuged, aliquoted into plasma, and stored in continuously monitored liquid nitrogen freezers (−130 °C or below) until used in immunoassays. More than 95% of the blood samples arrived in our laboratory within 26 hours of phlebotomy. Details regarding blood collection, processing and storage of plasma aliquots within these two cohorts have been previously described (30, 31).

Identification of study participants

Individuals with incident CRC through 2010 follow-up were eligible for this study if they provided a prediagnostic blood specimen, completed the baseline questionnaire, and did not have a history of inflammatory bowel disease or other cancer (except non-melanoma skin cancer) prior to diagnosis of CRC. We obtained written permission from participants who reported a diagnosis of CRC to retrieve their medical and pathology reports. Study physicians who were blinded to the exposure data reviewed all the records and verified the tumor location, stage and histologic subtype. We searched deaths of non-respondents

through the National Death Index (NDI) and further determined whether the deceased participant had a prior diagnosis of CRC (32, 33). Through this process, we identified 347 CRC cases in the NHS and 274 CRC cases in the HPFS cohorts.

Ascertainment of death

We identified deaths through next-of-kin and the NDI. Mortality follow-up was more than 98% complete (32, 33). For all deaths, we sought information to determine the cause through review of death certificates and medical records.

Laboratory Analyses

Plasma levels of adiponectin for all the participants were measured using enzyme-linked immunosorbent assays (ELISA) from ALPCO Diagnostics (34). In order to assess laboratory precision, quality control samples were interspersed randomly among the case-control samples. This generated an interbatch coefficient of variation of 8.6%. All assays were conducted by personnel blinded to the quality control status and participants' information. In a subset of participants, we also previously measured adiponectin using a separate ELISA from LINCO (31). For these participants, we observed a correlation of 0.79 between the two assay methods. Analysis of the biomarkers was achieved in a single run in HPFS and two runs in NHS. The run specific cut-off points were used for association analysis in the NHS to account for laboratory variation. Details regarding measurements of other biomarkers including high sensitivity C-reactive protein (CRP), IL-6, the soluble tumor necrosis factor receptor 2 (sTNFR2; TNFRSF1B), insulin-like growth factor (IGF)-1 and IGF-binding protein (IGFBP)-3 have been described in our prior studies (35, 36).

Statistical Analyses

We categorized plasma adiponectin level into quartiles based on the known distribution of adiponectin levels among a cohort of controls without cancer, that were matched to the cases of CRC in the present study (25).We calculated means (standard deviation, SD), medians (interquartile ranges, IQR) and proportions for baseline characteristics of study participants in each quartile of adiponectin at the time of blood draw. Analysis of variance for continuous variables and Chi-square tests for categorical variables were used to evaluate differences across quartiles. Cox proportional hazards model was used to calculate hazard ratio (HR) and 95% confidence interval (CI) for CRC-specific and overall mortality associated with each quartile of adiponectin. We conducted age-adjusted and multivariate analyses, stratified by age and adjusting for other predictors of survival (date of blood draw, cohort (sex), ethnicity, body mass index (BMI) at time of blood draw, physical activity (MET-hours/week) at time of blood draw, current or past smoking, dietary factors (consumption of alcohol, folate, calcium and red meat), family history of CRC, regular use of aspirin/NSAIDS, stage at diagnosis, grade (poor/unknown vs. well vs. moderate), site of primary cancer (colon vs. rectum), inflammatory markers (CRP, IL-6 and sTNFR2), and IGF-1/IGFBP-3 ratio. Tests for linear trend were conducted using the median value of each quartile as a continuous variable in the regression models. The proportionality hazards assumption for covariates was tested by the Harrell and Lee test (37).

Further analyses were performed according to selected subgroups (age at blood draw, gender, BMI, site of primary tumor, stage at diagnosis and histological grade) to determine if they modified the association of adiponectin and survival. Tests of interactions between adiponectin and potentially modifying covariates were assessed by entering in the models the cross product of adiponectin with the covariate of interest and assessing their significance using the Wald test. All statistical tests were two sided and a P value of < 0.05 was assumed for statistical significance. All analyses were performed using SAS v. 9.3 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

Among the 621 eligible participants, there were 269 (43%) total deaths, of which 181 (67%) were due to CRC. The median follow-up time for participants who were alive through the end of follow-up from date of diagnosis was 9.1 years (IQR, 6.1–12.1). Plasma collection was performed at a median of 9.8 years (SD 5.0 years) for NHS and 6.3 years (SD 3.6 years) for HPFS before diagnosis of CRC. Baseline characteristics according to quartiles of plasma adiponectin are illustrated in Table 1. Patients with higher quartiles of adiponectin were older at the time of diagnosis ($P = 0.03$), had lower BMI ($P < 0.001$) and presented with higher grade tumors ($P = 0.005$).

Plasma adiponectin and mortality

We examined the association of prediagnostic plasma adiponectin with CRC-specific and overall mortality. Compared with participants with levels of plasma adiponectin in the lowest quartile, the multivariate HRs for CRC-specific mortality were 1.18 (95% CI, 0.75–1.86) for those in the second quartile, 1.24 (95% CI, 0.78–1.98) for those in the third quartile and 1.89 (95% CI, 1.21–2.97) for those in the highest quartile ($P_{trend} = 0.01$) (Table 2). The corresponding multivariate HRs for overall mortality for participants with adiponectin levels in the second quartile of adiponectin were 0.94 (95% CI, 0.65–1.36), 1.08 (95% CI, 0.75–1.56) for the third quartile and 1.66 (95% CI, 1.15–2.39) for the highest quartile ($P_{trend} = 0.009$), when compared to those with adiponectin levels in the lowest quartile (Table 2).

We subsequently conducted analyses according to selected subgroups to assess if the association between adiponectin and mortality differed according to other predictors of survival defined by age, sex, BMI, stage, grade and site of primary cancer (Table 3). The influence of plasma adiponectin on CRC-specific mortality seemed to be more pronounced in patients with metastatic disease (HR 3.02; 95% CI, 1.50–6.08), comparing extreme quartiles of adiponectin ($P_{interaction} = 0.026$). In addition, we observed consistent results among patients who were diagnosed less than two years after blood collection and those who were diagnosed two or more years after blood collection. ($P_{interaction} = 0.66$). Comparing extreme quartiles of adiponectin, participants who were diagnosed less than two years after blood collection had a multivariate HR for CRC-specific mortality of 3.40 (95% CI, 1.03–11.2; $P_{trend} = 0.036$). The corresponding multivariate HR for those who were diagnosed two or more years after blood collection was 1.77 (95% CI, 1.11–2.84, $P_{trend} = 0.023$).

Discussion

In this prospective cohort study, we demonstrated that higher levels of prediagnostic circulating adiponectin were associated with adverse survival among CRC patients, with an approximately 2-fold higher risk of CRC-specific mortality and 1.7-fold higher risk of overall mortality, after adjusting for other potential determinants of mortality, including BMI. These results suggest that plasma adiponectin is likely to be an independent prognostic factor. Further subgroup analyses revealed that participants with metastatic disease appeared to have the greatest increase in risk of CRC-specific mortality.

The potential pleiotropic roles of adiponectin have generated much controversy. Adiponectin has been demonstrated to possess anti-carcinogenic effects via both direct and indirect mechanisms. *In-vitro* studies have shown that activation of the AMPK pathway in cancer cells, with consequent downregulation of mechanistic target of rapamycin (MTOR) and increased expression of cyclin-dependent kinase inhibitors p21 and p27 is responsible for its anti-proliferative and apoptotic effects (14). Furthermore, adiponectin exerts a direct inhibitory effect on the PI3K/AKT pathway, an important intracellular signalling pathway responsible for regulating cell cycling, proliferation, and survival (15). Its indirect actions comprise of modulation of insulin sensitization and inflammation. Chronic hyperinsulinemia and insulin resistance have been established as one of the etiologic links between obesity and colon cancer (16). Adiponectin has been demonstrated to exert a profound insulin-sensitizing effect through activation of AMPK and peroxisome proliferator-activated receptor alpha (PPAR-α) pathways in xenograft models, with resultant inhibition of tumor growth and angiogenesis (38). In addition, adiponectin mediates the production of anti-inflammatory cytokines such as IL-10 and metalloproteinase-1 inhibitor, inhibition of pro-inflammatory chemokines and adipokines such as IL-6 and TNF-α, inhibition of myelomonocytic precursor cells (mediators of innate immunity) and downregulation of T and B-cell recruitment, all of which serve to impede inflammation-induced oncogenesis (17).

In contrast, other studies have reported adiponectin's pro-carcinogenic properties. It has been shown to stimulate the production of pro-inflammatory cytokines such as IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and inhibit apoptosis via activation of AMPK/SIRT1/PGC-1α (19). In addition, it has been demonstrated to possess pro-angiogenic activity in mouse models (21). Lastly, adiponectin has been shown to promote colonic cell proliferation in a dose-dependent manner (18).

Several epidemiologic studies have demonstrated that higher circulating adiponectin is associated with a significant reduction in the risk of developing CRC (22–25). Results from a meta-analysis of 9 studies demonstrated a significant inverse relationship between plasma adiponectin and CRC (OR 0.91, 95% CI, 0.83–1.00; P = 0.04) (24). This is consistent with the results from another meta-analysis of 13 studies that included 2,632 cases of CRC or adenoma and 2753 healthy controls (23). However, a recent meta-analysis of 26 studies demonstrated that an increment of 1 mg/L in circulating adiponectin was significantly associated with a 20–30% increased risk of CRC (39).

Studies assessing the potential impact of circulating adiponectin on CRC survival are comparatively limited. The only prospective study revealed that plasma adiponectin was not a significant predictor of CRC survival (HR 1.00; 95% CI, 0.97–1.04; p = 0.94) (26). However, in this study, plasma adiponectin was measured at the time of diagnosis of CRC rather than pre-diagnostically. To our knowledge, our study is the first to examine the relationship between plasma adiponectin measured prior to CRC diagnosis and survival in CRC patients.

Because prior studies have suggested a protective effect of higher circulating adiponectin on the development of incident CRC, our results showing that prediagnostic circulating adiponectin is significantly associated with worse prognosis among patients with CRC may initially appear inconsistent. However, similar findings have been reported for other gastrointestinal cancers such as hepatocellular carcinoma (HCC). Recently, Siegal et al. demonstrated that higher serum adiponectin level at the time of diagnosis of HCC is associated with worse OS (HR 1.90; 95% CI, 1.05–3.45; P = 0.03) (27).

Several hypotheses may account for our findings. First, it is possible that a high level of circulating adiponectin is associated with a lower incidence of CRC, but individuals who develop CRC despite elevated adiponectin levels may be predisposed to tumors that arise through distinct mechanisms. These tumors may have adverse features associated with poor prognosis that could explain our findings. Second, although several *in-vitro* and *in-vivo* studies suggest that adiponectin exerts an anti-inflammatory effect (40, 41), additional studies have refuted this notion, particularly in the setting of chronic conditions such as inflammatory bowel disease (42) and rheumatoid arthritis (43). Hence, it is possible that the inflammatory microenvironment generated by the predominance of pro-inflammatory factors, which is mediated by adiponectin, in the setting of individuals with cancer may facilitate tumor proliferation and metastasis, thus leading to worse survival (44, 45). Furthermore, a study conducted in adiponectin transgenic mice showed that elevated levels of adiponectin do not protect against CRC development (46). Third, emerging evidence has demonstrated that adiponectin exerts potent anti-apoptotic effect via activation of the AMPK/Sirtuin 1 (SIRT1)/PGC-1α pathway, leading to increased mitochondrial gene expression and cell proliferation (19). Lastly, adiponectin has been associated with a lower risk of development of fatty liver (47). Several studies have supported a potential protective effect conferred by fatty liver against hepatic metastasis via inhibition of angiogenesis (48). Hence, patients with low adiponectin levels may be relatively protected against the development of hepatic metastasis and thus better prognosis in the absence of metastatic disease elsewhere.

The strengths of our study include large sample size, prospective design, detailed epidemiologic data, high follow-up rates, and high accuracy of self-reported data since our cohort participants comprise of health professionals. Several limitations warrant comment in our study. We were unable to distinguish between HMW and LMW adiponectin. There is some suggestion that HMW adiponectin, being the more biologically active form, may be a better predictor of CRC risk (49). The two isoforms also possess inherent differences with respect to inflammation, with HMW adiponectin being pro-inflammatory and LMW adiponectin anti-inflammatory. Furthermore, information on cancer recurrence and relapse

were not available in these cohorts. However, CRC-specific survival should be a reasonable surrogate for recurrence as the median survival for recurrent CRC was approximately 10–12 months during the time period of this study. We also had limited data on treatment. However, it is unlikely that the heterogeneity in treatment during the time period under study could explain the observed results. The treatment paradigm did not change significantly during this period and receipt of chemotherapy was largely defined according to stage, which we accounted for in our analysis. In addition, our analysis used a single measurement of adiponectin drawn prior to CRC diagnosis. However, previous studies have established that adiponectin levels remain stable over time (36), and given the prospective design of our study, any measurement error in adiponectin level would likely attenuate our observed associations. We also did not measure adiponectin levels after diagnosis. Thus, we were unable to examine the association of adiponectin with survival according to levels prediagnosis compared with postdiagnosis. Finally, the generalizability of our results to other populations may be limited as our participants were restricted to healthcare professionals.

In conclusion, our study provides evidence that higher levels of prediagnostic plasma adiponectin are associated with increased risk of CRC-specific and overall mortality in patients with CRC. Our findings support the notion that plasma adiponectin may play a distinct biological role in the progression of CRC compared with its development. Additional prospective studies are warranted to fully elucidate the underlying biological mechanisms of adiponectin and its associated pathways, and determine its clinical and prognostic utility in CRC.

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Table 1

Baseline characteristics of study participants according to quartiles of prediagnostic plasma adiponectin

	Quartiles of plasma adiponectin			
Characteristic	**1 (n=196)**	**2 (n=134)**	**3 (n=151)**	**4 (n=140)**
Age at diagnosis, y, mean (SD)	68.8 (8.7)	69.6 (7.7)	70.8 (8.6)	71.3 (7.8)
Body mass index, kg/m^2, mean (SD)	27.3 (4.4)	26.8 (4.5)	25.4 (3.6)	24.3 (3.6)
Gender				
Males, %	46	46	50	34
Females, %	54	54	50	66
Race				
White, %	94	96	94	99
Other, %	6	4	6	1
Smoking status				
Current or past, %	59	51	58	57
Never, %	41	49	42	43
Physical activity, METs, mean (SD)	20.3 (18.3)	22.7 (22.8)	24.4 (25.9)	24.4 (25.6)
Regular use of aspirin or NSAIDs, ≥2 tablets/week, %	51	37	50	49
Year of CRC diagnosis, y, mean (SD)	2000 (4)	2000 (5)	1999 (4)	1999 (5)
Tumor location, %				
Colon	91	85	88	89
Rectum	9	15	12	11
Stage of Disease, %				
I	27	30	30	24
II	24	21	21	25
III	20	19	17	24
IV	12	15	13	16
Other/unknown	17	16	19	12
Grade of differentiation, %				
Well	6	15	17	6
Moderate	62	47	51	60
Poor/undifferentiated	13	16	11	18
Unknown	19	22	22	16

METs = metabolic equivalent task score hours per week; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; CRC = colorectal cancer

Table 2

Overall and colorectal cancer-specific mortality according to quartiles of prediagnostic plasma adiponectin

	Quartiles of plasma adiponectin[a]				
Variable	**1**	**2**	**3**	**4**	P_{trend}[b]
Overall mortality (n=621)					
No. of events/ No. at risk	75/196	54/134	63/151	77/140	
Age-adjusted HR	1	0.98	1.06	1.39	0.07
95% CI	Referent	0.69–1.40	0.75–1.48	1.01–1.92	
MV-adjusted HR	1	0.91	1.04	1.51	0.024
95% CI[c]	Referent	0.63–1.31	0.73–1.48	1.08–2.12	
MV-adjusted HR	1	0.94	1.05	1.70	0.007
95% CI[d]	Referent	0.65–1.35	0.73–1.52	1.18–2.44	
MV-adjusted HR	1	0.94	1.09	1.68	0.007
95% CI[e]	Referent	0.65–1.36	0.75–1.57	1.16–2.41	
MV-adjusted HR	1	0.94	1.08	1.66	0.009
95% CI[f]	Referent	0.65–1.36	0.75–1.56	1.15–2.39	
CRC-specific mortality (n=621)					
No. of events/ No. at risk	49/196	38/134	44/151	50/140	
Age-adjusted HR	1	1.12	1.15	1.54	0.025
95% CI	Referent	0.73–1.72	0.76–1.74	1.03–2.29	
MV-adjusted HR	1	1.10	1.18	1.77	0.013
95% CI[c]	Referent	0.71–1.71	0.76–1.83	1.16–2.68	
MV-adjusted HR	1	1.17	1.24	1.97	0.006
95% CI[d]	Referent	0.75–1.85	0.78–1.97	1.25–3.09	
MV-adjusted HR	1	1.19	1.24	1.92	0.008
95% CI[e]	Referent	0.76–1.87	0.78–1.97	1.23–3.02	
MV-adjusted HR	1	1.18	1.24	1.89	0.01
95% CI[f]	Referent	0.75–1.86	0.78–1.98	1.21–2.97	

[a] Quartiles of plasma adiponectin were calculated separately within each cohort based on the distribution among controls based on previously collected data.

[b] Tests for linear trend were conducted using the median values for each quartile of adiponectin.

[c] Multivariate models were stratified by age at diagnosis, and adjusted for date of blood draw, sex, site of primary cancer (colon vs. rectum), stage at diagnosis and histological grade of cancer (well, moderate, poor/unknown).

[d] Multivariate models were stratified by age at diagnosis, and adjusted for date of blood draw, sex, site of primary cancer (colon vs. rectum), stage at diagnosis, histological grade of cancer (well, moderate, poor/unknown), body mass index (BMI), physical activity (metabolic equivalent task score hours per week (METS)), current or past smoking (yes or no), folate, calcium, alcohol, servings of red meat as a main dish, history of colorectal cancer in parent or sibling, and regular use of aspirin or NSAIDs (≥ 2 tablets per week).

[e] Multivariate models additionally adjusted for plasma CRP, sTNFR2 and IL-6, as well as the factors listed in d.

[f] Multivariate models additionally adjusted for plasma IGF-1/IGFBP-3, as well as the factors listed in e.

Table 3

Subgroup analyses of colorectal cancer-specific mortality according to quartiles of adiponectin

		Quartiles of plasma adiponectin					
Subgroup		**1**	**2**	**3**	**4**	P_{trend}	$P_{interaction}$
Low Age[a] (n=307)	No. of events/No. at risk	27/111	18/71	14/72	22/53		
	MV HR	1	1.32	1.32	2.24	0.002	
	95% CI	Ref	0.71–2.46	0.67–2.60	1.21–4.12		0.19
High Age[b] (n=314)	No. of events/No. at risk	22/85	20/63	30/79	28/87		
	MV HR	1	1.01	1.14	1.45	0.55	
	95% CI	Ref	0.54–1.90	0.63–2.07	0.81–2.62		
Male (n=274)	No. of events/No. at risk	15/90	16/61	24/75	16/48		
	MV HR	1	1.65	2.09	2.27	0.006	
	95% CI	Ref	0.80–3.38	1.08–4.06	1.10–4.71		0.54
Female (n=347)	No. of events/No. at risk	34/106	22/73	20/76	34/92		
	MV HR	1	0.99	0.84	1.24	0.14	
	95% CI	Ref	0.57–1.72	0.47–1.48	0.74–2.07		
Stage I/II/III tumors (n=536)	No. of events/No. at risk	29/173	21/114	26/131	28/118		
	MV HR	1	1.04	1.18	1.44	0.19	
	95% CI	Ref	0.59–1.86	0.69–2.04	0.83–2.50		0.026
Stage IV tumors (n=85)	No. of events/No. at risk	20/23	17/20	18/20	22/22		
	MV HR	1	1.29	1.13	3.02	0.003	
	95% CI	Ref	0.62–2.67	0.52–2.45	1.50–6.08		
Normal BMI[c](n=285)	No. of events/No. at risk	19/66	13/50	28/79	34/90		
	MV HR	1	0.92	1.51	1.84	0.05	
	95% CI	Ref	0.44–1.95	0.80–2.87	0.99–3.42		0.77
Overweight or Obese[d] (n=336)	No. of events/No. at risk	30/130	25/84	16/72	16/50		
	MV HR	1	1.39	0.92	1.86	0.09	
	95% CI	Ref	0.80–2.41	0.47–1.78	0.98–3.53		
Well or moderate grade (n=410)	No. of events/No. at risk	24/132	21/83	23/102	25/93		
	MV HR	1	1.03	1.33	1.83	0.07	0.50

		Quartiles of plasma adiponectin					
Subgroup		**1**	**2**	**3**	**4**	**P_{trend}**	**$P_{interaction}$**
	95% CI	Ref	0.54–1.96	0.71–2.49	0.97–3.45		
Poor or undifferentiated grade (n=89)	No. of events/No. at risk	12/26	8/22	10/16	13/25		
	MV HR	1	1.22	2.89	1.39	0.43	
	95% CI	Ref	0.46–3.26	1.11–7.57	0.58–3.34		
Colon (n=549)	No. of events/No. at risk	44/178	32/114	41/133	46/124		
	MV HR	1	1.22	1.35	1.99	0.006	
	95% CI	Ref	0.75–1.98	0.83–2.19	1.25–3.17		0.89
Rectum (n=72)	No. of events/No. at risk	5/18	6/20	3/18	4/16		
	MV HR	1	0.76	0.51	0.97	0.85	
	95% CI	Ref	0.22–2.66	0.11–2.26	0.24–3.83		

[a] Low age defined as below the median at blood draw (<60 for women and < 68 for men).

[b] High age defined as above the median at blood draw (≥ 60 for women and ≥ 68 for men).

[c] Normal body mass index (BMI) defined as <25.0 kg/m^2 based on World Health Organization (WHO) classification.

[d] Overweight and Obese defined as ≥25.0 kg/m^2 based on WHO classification.

Multivariate models were adjusted for age at diagnosis, date of blood draw, sex, site of primary cancer (colon vs. rectum), stage at diagnosis, histological grade of cancer (well, moderate, poor/unknown), body mass index (BMI), physical activity (metabolic equivalent task score hours per week (METS)), current or past smoking (yes or no), folate, calcium, alcohol, servings of red meat as a main dish, history of colorectal cancer in parent or sibling, regular use of aspirin or NSAIDs (≥ 2 tablets per week), CRP, sTNFR2, IL-6 and plasma IGF-1/IGFBP-3. For each stratified analysis, the stratification variable was omitted from the model.