Title:

Higher Circulating Adiponectin Concentrations Predict Incident Cancer in Type 2 Diabetes – The Adiponectin Paradox

Short running title:

Higher adiponectin level predicts cancer in diabetes

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Disclosures:

All authors have no conflicts of interest.

Keywords (MeSH):

Adiponectin, Type 2 Diabetes Mellitus, Prediction model, Cancer

Word Count: 249 words (Abstract) and 3372 words (Main text)

Abstract

Introduction

Despite the beneficial cardiometabolic effects of adiponectin demonstrated in preclinical studies, paradoxically, higher circulating adiponectin concentrations has been found, in epidemiological studies, to be associated with incident cardiovascular events, renal outcomes, as well as mortality, in patients with diabetes. On the other hand, diabetes is also associated with an increased risk of cancer. Here, we investigated prospectively the association between circulating adiponectin concentrations and incident cancer, using a cohort of exclusively individuals with type 2 diabetes.

Materials & Methods

Baseline serum adiponectin concentrations were measured in 5658 participants, recruited from the Hong Kong West Diabetes Registry. The associations of circulating adiponectin concentrations with incident cancer and cancer-related deaths were evaluated using multivariable Cox regression analysis, with hazard ratio (HR) for adiponectin referring to the respective risk per doubling of serum adiponectin concentration.

Results

Over a median-follow up of around 6.5 years, 7.53% and 3% of participants developed cancer and had cancer-related deaths, respectively. Serum adiponectin concentrations

were significantly higher in those who had incident cancer (9.8 ug/ml vs 9.1 ug/ml, p<0.001) and cancer-related deaths (11.5 ug/ml vs. 9.3 ug/ml, p<0.001) compared to those without. Moreover, in multivariable analyses, serum adiponectin concentration was independently associated with both incident cancer (HR 1.19, 95%CI 1.05-1.35, p=0.006) and cancer-related deaths (HR 1.23, 95%CI 1.03-1.47, p=0.024).

Conclusions

Higher serum adiponectin concentration was independently associated with incident cancer and cancer-related deaths in type 2 diabetes, indicating that adiponectin paradox can be observed in another major diabetic complication in addition to cardiovascular and kidney diseases.

Introduction

Type 2 diabetes mellitus is associated with an increased risk of cancer. (1) In a recent meta-analysis of more than 19 million individuals from 121 cohorts, diabetes was associated with an excess risk of 27% in women and 19% in men for all-site cancers. (2) Moreover, in contrast to the reduced cardiovascular mortality observed over the last decade, cancer related deaths among individuals with diabetes have not improved significantly. (3)

Adiponectin is an adipocyte-derived hormone with anti-inflammatory, insulin-sensitizing, vasoprotective, reno-protective properties demonstrated in rodents and cell-based studies. (4) (5) Whether it has similar beneficial effects in humans, however, remain unclear. In epidemiological studies, low circulating adiponectin concentrations have been associated with the development of type 2 diabetes, (6) (7) but more recent Mendelian association studies do not support the causative role of hypoadiponectinemia in insulin resistance or type 2 diabetes. (8) On the other hand, while conflicting associations between circulating adiponectin concentrations and cardiovascular outcomes have been observed in population-based studies, (9) (10) (11) (12) the majority of studies conducted in patients with established cardiovascular and/or renal diseases have reported the association of high circulating adiponectin concentrations with adverse cardiovascular outcomes and all-cause mortality, suggesting the

"adiponectin paradox".(12) (13) (14) In diabetes, a U-shaped association has been observed on the relationship between serum adiponectin concentrations and incident cardiovascular disease.(15) Moreover, high adiponectin concentrations were also found to be a predictor of adverse renal outcomes in patients with type 1 diabetes, (16) (17) and more recently, in those with non-diabetic chronic kidney disease as well.(18)

In the context of cancer, although preclinical studies have shown that adiponectin directly impacts on various signalling pathways involved in protein synthesis, cell growth, proliferation and survival, (19) the relationship between circulating adiponectin concentrations and cancers remains controversial. While most studies have demonstrated no or inverse association between serum adiponectin concentrations and cancer, (19) (20) (21) a few recent studies have also found serum adiponectin concentrations to be associated with an increased risk of liver cancer and worse cancer survival. (22) (23) Therefore, we performed this prospective study to investigate the prognostic implication of a higher serum adiponectin concentration in terms of cancer risk in diabetes, and whether the adiponectin paradox could also be observed in the development of cancer and cancer deaths among individuals with type 2 diabetes, using a large clinic-based cohort of Chinese individuals.

Materials & Methods

Study Participants

All participants were recruited from the Hong Kong West Diabetes Registry (HKWDR), which consisted of patients who had type 2 diabetes and were being followed up regularly at the medical specialist clinics of the Hong Kong West Cluster since 2008. At enrolment to the registry, all Chinese patients were consecutively invited to participate in a prospective cohort study that aimed to identify risk factors, which included genetic and serum biomarkers, that predispose to the development of diabetic complications. Informed consent was obtained in around 85% of the invited patients. Type 2 diabetes was diagnosed by physicians, based on clinical history, biochemical and/or immunological findings. During each visit, participants were assessed clinically and had laboratory investigations to determine their control of diabetes, its related cardiovascular risk factors, and the presence of diabetic complications. The study protocol was approved by the institutional review board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster. In this study which evaluated the relationship between circulating adiponectin concentrations and cancer-related outcomes, only participants who had follow-up for more than one year after recruitment to the prospective cohort study were included for analysis, in order to minimize the possibility of reverse causality. Moreover, in the analysis examining the association

between circulating adiponectin concentrations and incident cancer, participants who had known history of cancer at baseline were also excluded.

Clinical and biochemical assessments

Participants attended each visit after an overnight fasting of at least 8 hours. At the baseline visit, demographic data, including age, sex, occupation, smoking, alcohol consumption, and physical activity were obtained. Detailed family, medical and drug histories were ascertained using a standardized questionnaire. Anthropometric parameters, including body weight, height, body mass index (BMI), waist circumference (WC), and blood pressure (BP) were measured. Fasting blood was drawn for plasma glucose, lipids and glycated hemoglobin (HbA1c). Serum creatinine was measured and the eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as described previously.(24) Serum high-sensitive C-reactive protein (hsCRP) concentration was measured with a high-sensitivity, particle-enhanced immune-turbidimetric assay (Roche Diagnostics, GmbH). Albuminuria status was assessed using at least two random urine samples on two separate occasions within six months, and categorized accordingly (urine albumin to creatinine ratio <30mg/g [A1], 30-300 mg/g [A2] and >300mg/g [A3]).(25)

ELISA for Quantitative Measurement of Human Adiponectin Concentrations

Serum adiponectin concentration was measured with a quantitative sandwich ELISA kit developed by our group (Antibody and Immunoassay Services, University of Hong Kong). (26) In brief, serum samples were diluted 100-fold before assay. Subsequently, 100 microliters each of diluted sera and standards were applied to a 96-well microtiter plates pre-coated with a mouse monoclonal antibody against human adiponectin. A standard curve was constructed by plotting the absorbance values at 450 nm against the adiponectin concentrations of the standards, while the concentrations of the samples were determined by use of this standard curve. The lowest concentration of adiponectin that could be detected by this assay was 1.56 ng/ml. The intra- and inter-assay coefficients of variations were 4.0% and 9.5%, respectively.

Definitions of outcomes

Incident cancer and cancer-related deaths, the two primary outcomes of this study, were retrieved from the Clinical Data and Analysis Reporting System of the Hospital Authority database as of 31st March 2019, based on diagnosis codes of the ninth edition of the International Classification of Diseases (ICD-9) (ICD-9 codes 140-195, 199-234). Incident cancer was defined as the first recorded diagnosis of cancer, whereas cancer-related death was defined as death event with cancer entered as the

principal diagnosis. The medical diagnoses were adjudicated and reviewed by two physicians independently, and disagreements between them, if any, were resolved by a third.

Statistical analysis

All data were analysed with SAS version 9.4 (SAS institute, Cary, NC). Data that were not normally distributed as determined using Kolmogorov-Smirnov test, which included serum adiponectin, triglyceride and hsCRP concentrations, were $\log_2$ transformed to obtain near normality before analysis. Values were reported as means ± standard deviation (SD), medians with 25^{th} and 75^{th} percentiles for variables with skewed data, or percentages, as appropriate. Multivariable Cox regression analysis was used to evaluate the associations of baseline circulating adiponectin concentrations with incident cancer and cancer-related deaths. Competing risk analysis was also performed in the evaluation of cancer-related deaths. The hazard ratio (HR) of circulating adiponectin concentration referred to the risk of incident cancer or cancer-related death per unit difference in the log-transformed, or a doubling of serum adiponectin concentration measured in ug/ml. All models were adjusted for the same set of variables, which included all that were statistically significant in univariate analyses of either incident cancer or cancer-related deaths. Proportional hazards assumption was checked

and verified using a global goodness-of fit test proposed by Schoenfeld (27). Interaction terms were checked in performing Cox regression analysis. The performance of the clinical model to predict incident cancer, with or without serum adiponectin concentrations, was examined using time-dependent C-statistics, net reclassification index (NRI) and integrated discrimination index (IDI). In all statistical tests, two-sided p-values <0.05 were considered significant.

Results

A total of 5658 participants with type 2 diabetes were included in our study. Among them, 396 participants had known history of cancer at baseline (the top five cancers, in descending order of their prevalence, were cancers of breast, colon, prostate, liver and rectum), and were excluded for the prospective observation for incident cancers, but were included in the analysis on cancer deaths.

Circulating adiponectin concentrations were significantly higher in those with history of cancer at baseline

At baseline, increasing tertiles of serum adiponectin concentrations were significantly associated with older age, being female, longer duration of diabetes, lower BMI, better glycemic control, lower levels of triglyceride and hsCRP, higher levels of

high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Moreover, higher serum adiponectin concentrations were significantly associated with lower eGFR levels and a higher prevalence of albuminuria, in keeping with findings reported from previous studies. (28) (29) Notably, we found that participants with history of cancer at baseline also had significantly higher serum adiponectin concentrations than those who did not. (Table 1)

Circulating adiponectin concentrations were significantly higher in those with incident cancer and cancer-related deaths

Over a median follow-up period of 6.5 years, 396 of the 5262 (7.53%) participants with no known cancer at baseline developed incident cancer (8.3% in men and 6.5% in women), with a cumulative incidence of 11.6 per 1000 person-years. The top five cancers, in descending order of their incidence, were cancers of lung (N=54 with 70% men; adenocarcinoma 58%, squamous cell carcinoma 15%, small cell carcinoma 9%, radiological 17%), colon (N=42 with 69% men), prostate (N=35), liver (N=31 with 81% men) and breast (N=30). On the other hand, 170 of 5658 participants (3%) had cancer-related deaths (3.3% in men and 2.6% in women), with a cumulative incidence of 4.57 per 1000 person-years.

Table 2 summarizes the baseline characteristics of the study participants with reference to incident cancer and cancer-related deaths. Participants who developed cancer were significantly older, being men and ever-smokers, and had a higher prevalence of hypertension, cardiovascular disease and albuminuria at baseline compared to those who did not. Moreover, there were significantly higher use of insulin, and lower use of metformin among those who had incident cancer, as well as significantly higher serum hsCRP, lower mean LDL-C and eGFR levels, compared to those who did not have incident cancer.

Similarly, participants who had cancer-related deaths were also more likely to be older, being ever-smokers, having a higher prevalence of background hypertension, cardiovascular disease, albuminuria and history of cancer, and lower baseline HbA1c and eGFR levels compared to those who did not. Serum hsCRP concentrations and use of insulin were similar between those with or without cancer-related deaths, although metformin users were significantly lower in those who had cancer-related deaths compared to those who did not.

Serum adiponectin concentrations were significantly higher in those who had incident cancer (9.8 ug/ml [7.1 – 15.0] vs. 9.1 ug/ml [6.1 – 13.7] for with and without incident cancer, respectively; $p < 0.001$) and also in those with cancer-related deaths

(11.5 ug/ml [7.8 – 18.8] vs. 9.3 ug/ml [6.2-13.9] for with and without cancer-related deaths, respectively; p<0.001).

Circulating adiponectin concentrations independently predicted incident cancer and cancer-related deaths

In multivariable Cox regression analyses, serum adiponectin concentration was independently associated with incident cancer (HR 1.19, 95%CI 1.05-1.35, p=0.006), together with age (HR 1.05, 95%CI 1.04-1.06, p<0.001), ever-smoking (HR 1.53, 95%CI 1.21-1.94, p<0.001), use of insulin (HR 1.36, 95%CI 1.09-1.69, p=0.007), and hsCRP concentration (HR 1.07, 95%CI 1.01-1.13, p=0.024) in a model consisting of other variables including sex, BMI, hypertension, cardiovascular disease, albuminuria, use of metformin, LDL-C and eGFR levels at baseline. (Table 3) Although a significant interaction was found between age and serum adiponectin with incident cancer, serum adiponectin concentration remained an independent predictor of incident cancer (p=0.002) after adjustment for the interaction term of age and adiponectin. Cumulative incidence curves depicting the association of incident cancers with increasing tertiles of serum adiponectin concentrations is shown in Figure 1.

Similarly, serum adiponectin concentration was independently associated with cancer-related deaths (HR 1.23, 95%CI 1.03-1.47, p=0.024), together with age (HR 1.04, 95%CI 1.03-1.06, p<0.001), ever-smoking (HR 1.67, 95%CI 1.14-2.44, p=0.009), and history of cancer at baseline (HR 4.08, 95%CI 2.87-5.79, p<0.001), in a model which included also sex, body mass index, hypertension, cardiovascular disease, albuminuria, use of metformin, HbA1c, hsCRP and eGFR levels at baseline. (Table 3) However, the association between serum adiponectin concentrations and cancer-related deaths became attenuated after excluding those with history of cancer at baseline (HR 1.12, 95%CI 0.92-1.38, p=0.270), which could probably be related to the low number of events among those without history of cancer at baseline. Moreover, in sex-specific analyses, serum adiponectin concentration was independently associated with incident cancer in men (HR 1.23, 95%CI 1.05-1.44, p=0.009) but not in women. For cancer-related deaths, serum adiponectin concentration was not significant in both men and women.

We further explored if serum adiponectin concentrations could be employed as a clinically useful marker to predict incident cancer in diabetes. However, the addition of serum adiponectin concentration to the clinical model, which consisted of age, sex, ever-smoking, hypertension, use of metformin and insulin, history of cardiovascular disease and cancer, albuminuria, HbA1c, LDL-C and eGFR levels at baseline, did not

result in any significant improvement in NRI (p=0.116), IDI (p=0.09), or time-dependent C-statistics (p=0.132).

Discussion

To our knowledge, our study was the first to demonstrate that, despite the anti-carcinogenic effects of adiponectin shown in preclinical studies, (30) higher circulating adiponectin concentration was associated with both incident cancer and cancer-related deaths in type 2 diabetes, suggesting another major diabetic complication in which the adiponectin paradox can be observed in addition to cardiovascular and kidney diseases.

Our findings were in contrast to the few previous studies that evaluated the relationship between circulating adiponectin concentrations and incident cancer or cancer-related deaths. For instance, in a prospective analysis of 3444 individuals (11.7% with diabetes) in the multi-ethnic Dallas Heart Study cohort, no association between plasma adiponectin concentrations and incident cancer was found. (21) Likewise, in another prospective study consisting of 950 men with type 2 diabetes, plasma levels of high-molecular weight (HMW) adiponectin were also not associated with cancer deaths. (12) We speculated that the discrepancy between our results and those reported from these studies could be attributed to differences in our study

population with exclusively individuals with type 2 diabetes, as well as our relatively larger sample size involving participants of both sexes.

The underlying reasons behind the adiponectin paradox remain largely unknown, although several mechanisms have been postulated over the years to explain this paradox as observed in cardio-renal diseases, which include a "failed" compensatory response, (31) adiponectin resistance, (32) decreased renal clearance of adiponectin, (5) and even potential deleterious effects of adiponectin. (33) For instance, in a previous study, 36 patients with advanced heart failure undergoing implantation of ventricular assistive device had significantly higher baseline serum adiponectin concentrations compared to the healthy controls, and their myocardial expressions of both adiponectin receptors AdipoR1 and AdipoR2, as well as the downstream target AMP kinase (AMPK) were found to have decreased. Importantly, all these changes reversed after the implantation of ventricular assistive device, suggesting that functional adiponectin resistance might have occurred in advanced heart failure. (32) On the other hand, in studies comparing patients with end-stage renal disease (ESRD) against normal controls with kidney function, those with ESRD had higher circulating adiponectin levels, (29) increased AdipoR1 expression in their skeletal muscle but disrupted downstream adiponectin signalling, suggesting the presence of adiponectin resistance at the post-recep3tor level in renal dysfunction. (34) Indeed, adiponectin resistance has

304 also been reported in obesity and diabetes. (5) (35) Reduced expressions of adiponectin
305 receptors have been observed in the skeletal muscle and adipose tissue of obese mice,
306 (36) as well as in the omental adipocytes of obese individuals. (37) Therefore, in our
307 study, the higher serum adiponectin concentrations in those with incident cancer and/or
308 cancer-related deaths might indicate the presence of adiponectin resistance at baseline,
309 which could be secondary to a combination of their pre-existing obesity, cardiovascular
310 and/or renal diseases, although these conditions on their own were not independently
311 associated with the development of cancer or cancer-related deaths in our study.

312 Our findings were however unlikely to be a consequence of impaired renal
313 excretion, since serum adiponectin concentrations of the participants remained
314 independently associated with incident cancer and cancer-related deaths even after
315 adjustments for their baseline eGFR levels. Moreover, in a previous study that
316 examined the paradoxical relationship between circulating adiponectin concentrations
317 and all-cause mortality in type 2 diabetes, subgroup analysis revealed significant
318 association in participants with relatively preserved kidney function (i.e. eGFR
319 $\geq$60ml/min/1.73m^2) rather than in those with eGFR <60ml/min/1.73m^2. (38)

320 On the other hand, while adiponectin is often hailed as a beneficial adipokine in
321 most studies, there are also reports suggesting that adiponectin could possess
322 deleterious effects, especially in chronic inflammatory conditions, where its

compensatory increase might become too overwhelming. (31) (13) In our study, the association between serum adiponectin concentration and incident cancer, being independent of baseline serum hsCRP concentration, argued against a compensatory upregulation of adiponectin in response to subclinical inflammation mediated by CRP, or its upstream pro-inflammatory cytokines. However, whether the higher adiponectin concentration was compensatory to the effects of other inflammatory pathways on adiponectin signalling, (35) remains to be elucidated. Moreover, some preclinical studies demonstrated pro-inflammatory effects of adiponectin both *in vitro* (39) and *in vivo*. (40) Higher serum adiponectin concentrations were also found in patients with rheumatoid arthritis and positively correlated with their disease severity and activity. (41) Adiponectin promoted angiogenesis, inflammation and joint destruction by stimulating vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP) in cultured synovial cells from patients with rheumatoid arthritis, as well as nuclear factor kappa B (NF-kB) in human chondrocytes. (42) Importantly, these inflammatory mediators were also implicated in obesity-related tumorigenesis.(19) Therefore, it remains possible that in diabetes, being a chronic inflammatory condition, (43) higher concentrations of adiponectin might also exert pro-inflammatory effects and increase the risk of cancer. Indeed, *in vitro* studies had previously found dichotomous

341 effects of adiponectin on cancer cell growth and proliferation, depending on the
342 oestrogen receptor α status in breast cancers. (44)

343 Our study had a few limitations. First, the observational cohort design of the
344 study precluded direct conclusion on the precise role of higher adiponectin
345 concentrations on tumorigenesis in diabetes, two conditions with complex pathogenic
346 mechanisms. Moreover, observational studies could be associated with biases and
347 residual confounding. Some potential confounders related to cancers, such as levels of
348 physical activity, menopausal status and use of hormone replacement therapy in women,
349 could not be adjusted for as these data were unavailable in our registry. Second,
350 although its HMW isoform is the most bioactive in relation to insulin sensitivity, (45)
351 only total adiponectin was measured in the study. Nonetheless, the relative role of
352 HMW adiponectin versus non-HMW adiponectin in the association with incident
353 cancer remains controversial. (20) Third, the observation period for incident cancers
354 was relatively short, and the number of events was insufficient to provide adequate
355 statistical power for examining the relationship between serum adiponectin
356 concentrations and individual cancer subtype, as well as for sex-specific analyses. It is
357 noteworthy that in our study, the number of incident cancers in men was considerably
358 higher than that in women, as a result of the larger number of men included as well as
359 their higher cumulative incidence, which could have contributed to the apparent sex-

specific difference in the association between serum adiponectin concentrations and the risk of incident cancer. Furthermore, since our cohort comprises exclusively individuals with type 2 diabetes and cardio-renal comorbidities, our findings might not be generalizable to study populations without diabetes or diabetic populations with less comorbidities. That said, the adiponectin paradox on cardiovascular and all-cause mortality has also been reported in non-diabetic individuals with cardio-renal diseases. (13) Nonetheless, further studies using a different and independent cohort are required to validate our findings. Last but not least, although the addition of serum adiponectin concentration did not significantly improve C-statistics, NRI or IDI in the prediction of incident cancer in diabetes, we demonstrated that, in view of the presence of the adiponectin paradox, a higher adiponectin concentration might not be always beneficial, but instead, could implicate an increased risk of incident cancer in diabetes, as well as an increased risk of cancer-related deaths in those with cancer.

Conclusion

Despite the anti-proliferative and anti-carcinogenic properties of adiponectin shown in cellular and animal-based studies, our study has provided the first report of an adiponectin paradox in relation to the development of both cancer incidence and cancer-related deaths in type 2 diabetes. Higher circulating adiponectin concentrations

could be a risk marker of incident cancer in type 2 diabetes. Further studies with sex-specific analyses are required not only to validate our clinical findings, but also to provide mechanistic insights as to whether this adiponectin paradox is causal to the development of cancer in type 2 diabetes.

Conflict of Interest Statement

All authors declare no conflicts of interest.

Acknowledgments

We thank Ms. Rachel Wong for her technical assistance in measurement of serum adiponectin concentrations among our participants with type 2 diabetes. This work was supported by the Collaborative Research Fund of the Hong Kong Research Grant Council (HKU2/CRF/12R).

Author Contributions

C.H.L. researched the data and wrote the manuscript. D.T.W.L., C.Y.Y.C., M.M.A.Y., W.S.C., and Y.C.W. researched the data. C.H.Y.F. performed statistical analyses. Y.C.W. and A.X. critically reviewed and edited the manuscript. K.S.L.L. initiated and

supervised the study, edited the manuscript and would take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1 Cumulative incidence of cancer stratified by the tertiles of serum adiponectin concentrations of the study participants after multivariable adjustments

Table 1 Association of baseline variables with increasing tertiles of serum adiponectin concentrations in all study participants

	Tertile 1: < 7.23 ug/ml	Tertile 2: 7.23 – 12.0 ug/ml	Tertile 3: ≥ 12.0 ug/ml	P for trend
Number	1882	1887	1889	--
Sex (Men), %	72.1	56.3	46.6	**<0.001**
Age, years	59.5±12.3	63.9±12.3	66.6±12.1	**<0.001**
Ever smoker, %	39.6	33.3	28.7	**<0.001**
Duration of diabetes, years	10.4±8.19	11.6±8.39	13.3±9.30	**<0.001**
Body mass index, kg/m^2	27.0±4.29	26.2±4.30	24.9±4.21	**<0.001**
Waist circumference, cm	91.8±11.6	89.2±11.7	95.1±11.8	**<0.001**
Comorbidities at baseline, %				
Hypertension	88.1	87.8	87.6	0.648
History of CVD at baseline	35.3	36.1	32.7	0.089
History of cancer at baseline	4.2	6.4	10.4	**<0.001**
Concomitant medications, %				
Insulin	29.6	26.1	33.7	0.830
Sulphonylurea	46.5	49.9	46.3	0.281
Metformin	84.3	78.3	62.7	**<0.001**
Thiazolidinedione	0.7	0.8	2.0	**0.031**
Statin	53.8	53.2	50.5	0.156
ACEI	53.5	50.1	48.8	**0.004**
ARB	15.9	17.6	16.7	0.247
Laboratory parameters				
HbA1c, %	7.70±1.36	7.61±1.40	7.51±1.41	**<0.001**
Fasting glucose, mg/dL	142±43.4	140±44.7	136±47.5	**<0.001**

HDL-C, mg/dL	40.9±10.2	46.3±12.2	54.9±16.0	**<0.001**
LDL-C, mg/dL	88.9±30.0	89.6±31.3	92.6±31.8	**0.001**
Triglyceride*, mg/dL	134 (96.5-191)	113 (82.4-160)	91.2 (68.2-128)	**<0.001**
eGFR, ml/min/1.73m^2	81.7±21.7	75.8±23.6	66.9±26.8	**<0.001**
Albuminuria, %	42.5	46.1	54.7	**<0.001**
hsCRP*, ug/ml	1.28 (0.59-3.05)	1.25 (0.53-2.95)	0.96 (0.40-2.53)	**<0.001**

*Log base 2-transformed before analysis; Values in **BOLD** were statistically significant.

Continuous data were presented as mean±SD or median (interquartile range).

CVD, cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol (LDL-C); hsCRP, high sensitive C-reactive protein.

Hypertension was defined as blood pressure ≥ 140 / 90 mmHg or on anti-hypertensive medications; Albuminuria category was classified according to urine albumin to creatinine ratio: A1 <30mg/g, A2 30-300 mg/g and A3 >300mg/g.

Conversion factors for glucose from mmol/liter to mg/dL x18; HDL / LDL-cholesterol from mmol/liter to mg/dL x38.9; Triglyceride from mmol/liter to mg/dL x88.2.

Table 2 Association between baseline characteristics of study participants with incident cancer and cancer-related deaths

Baseline parameters	Incident cancer				Cancer-related death			
	Yes	No	Crude HR (95% CI)	p-value	Yes	No	Crude HR (95% CI)	p-value
N	396	4866	--	--	170	5488	--	--
Men, %	64.6	58.3	1.29 (1.04-1.61)	**0.014**	63.5	58.1	1.24 (0.91-1.69)	0.180
Age, years	68.6±11.3	62.5±12.6	1.06 (1.05-1.07)	**<0.001**	70.0±11.1	63.1±12.6	1.05 (1.04-1.07)	**<0.001**
Ever smoker, %	45.0	33.0	1.66 (1.35-2.05)	**<0.001**	46.5	33.5	1.71 (1.26-2.31)	**<0.001**
Duration of diabetes, years	12.3±8.7	11.6±8.6	1.01 (1.00-1.02)	0.075	13.0±9.5	11.7±8.7	1.01 (1.00-1.03)	0.090
Body mass index, kg/m^2	25.8±4.1	26.1±4.4	0.98 (0.96-1.01)	0.225	25.3±4.3	26.0±4.4	0.96 (0.92-1.00)	**0.043**
Waist circumference, cm	89.2±12.0	88.9±12.1	1.00 (0.99-1.01)	0.737	88.5±11.5	88.7±12.0	1.00 (0.99-1.01)	0.678
Comorbidities at baseline, %								
Hypertension	93.4	87.3	2.30 (1.54-3.43)	**<0.001**	92.4	87.7	1.82 (1.03-3.20)	**0.038**
History of CVD	44.2	33.8	1.70 (1.39-2.08)	**<0.001**	41.8	34.5	1.44 (1.06-1.96)	**0.018**
History of cancer	--	--	--	--	27.1	6.40	5.44 (3.87-7.65)	**<0.001**
Concomitant medications, %								
Insulin	34.8	29.2	1.25 (1.02-1.54)	**0.034**	34.8	29.2	1.15 (0.83-1.58)	0.400
Sulphonylurea	47.2	47.6	0.99 (0.81-1.20)	0.897	52.4	47.5	1.23 (0.91-1.66)	0.180
Metformin	71.2	76.5	0.68 (0.55-0.85)	**0.001**	62.7	75.2	0.54 (0.40-0.74)	**<0.001**
Thiazolidinedione	1.3	1.2	0.90 (0.37-2.18)	0.900	1.2	1.2	0.91 (0.24-3.67)	0.890
Statin	56.1	52.3	1.22 (1.00-1.49)	0.055	54.7	52.4	1.12 (0.83-1.52)	0.450
ACEI	55.8	50.9	1.18 (0.97-1.44)	0.102	55.3	50.6	1.17 (0.86-1.58)	0.320
ARB	16.4	16.6	1.03 (0.79-1.35)	0.812	17.1	16.7	1.06 (0.95-1.57)	0.790
Laboratory parameters								
HbA1c, %	7.7±1.5	7.6±1.4	0.99 (0.62-1.06)	0.702	7.5±1.5	7.6±1.4	0.88 (0.77-1.01)	0.071
HDL-C, mg/dL	46.8±14.2	47.3±14.2	1.00 (0.99-1.01)	0.583	48.0±14.0	47.4±14.4	1.00 (0.99-1.01)	0.500
LDL-C, mg/dL	86.9±30.5	90.8±31.2	0.99 (0.99-1.00)	**<0.001**	89.2±32.4	90.4±31.0	1.00 (0.99-1.00)	0.300
Triglyceride*, mg/dL	110 (79-160)	112 (80-160)	0.95 (0.79-1.15)	0.616	105 (78-160)	112 (80-160)	0.88 (0.72-1.08)	0.224
Fasting glucose, mg/dL	138.0±46.8	140.0±45.2	1.00 (1.00 – 1.00)	0.327	141.0±45.6	139.0±45.3	1.00 (1.00-1.00)	0.860
eGFR, ml/min/1.73m^2	68.3±22.9	75.9±24.8	0.99 (0.98-0.99)	**<0.001**	65.3±22.4	75.1±24.9	0.99 (0.98-0.99)	**<0.001**
Albuminuria (A2 or above), %	51.0	46.8	1.28 (1.05-1.56)	**0.013**	55.9	47.8	1.42 (1.05-1.92)	**0.022**
Adiponectin*, ug/ml	9.8 (7.1-15.0)	9.1 (6.1-13.7)	1.27 (1.14-1.41)	**<0.001**	11.5 (7.8-18.8)	9.3 (6.2-13.9)	1.53 (1.30-1.79)	**<0.001**
hsCRP*, ug/ml	1.17 (0.51-3.38)	1.12 (0.49-2.75)	1.06 (1.01-1.12)	**0.022**	1.32 (0.46-3.90)	1.14 (0.50-2.82)	1.06 (0.98-1.15)	0.153

*Log base 2-transformed before analysis; Hazard ratio for adiponectin referred to the respective risk per doubling of serum adiponectin concentration in ug/ml. Values in **BOLD** were statistically significant.

Continuous data were presented as mean±SD or median (interquartile range).

HR, hazard ratio; 95%CI, 95% confidence interval; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol (LDL-C); hsCRP, high sensitive C-reactive protein.

Hypertension was defined as blood pressure ≥ 140 / 90 mmHg or on anti-hypertensive medications; Albuminuria category was classified according to urine albumin to creatinine ratio: A1 <30mg/g, A2 30-300 mg/g and A3 >300mg/g.

Conversion factors for glucose from mmol/liter to mg/dL x18; HDL / LDL-cholesterol from mmol/liter to mg/dL x38.9; Triglyceride from mmol/liter to mg/dL x88.2.

Table 3 Multivariable Cox regression analyses showing the associations between serum adiponectin concentrations with incident cancer and cancer-related deaths

Baseline parameters	Incident Cancer (N=5262)		Cancer related death* (N=5658)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex (Men), %	1.19 (0.93-1.53)	0.166	1.09 (0.74-1.63)	0.660
Age, years	**1.05 (1.04-1.06)**	**<0.001**	**1.04 (1.03-1.06)**	**<0.001**
Ever-smoking, %	**1.53 (1.21-1.94)**	**<0.001**	**1.67 (1.14-2.44)**	**0.009**
BMI, kg/m^2	1.00 (0.98-1.03)	0.809	0.99 (0.94-1.03)	0.550
Hypertension, %	1.25 (0.82-1.92)	0.302	1.13 (0.61-2.07)	0.700
Cardiovascular disease at baseline, %	1.13 (0.90-1.41)	0.284	1.01 (0.72-1.40)	0.980
History of cancer at baseline, %	--	--	**4.08 (2.87-5.79)**	**<0.001**
Use of metformin, %	1.03 (0.80-1.33)	0.822	0.85 (0.56-1.29)	0.450
Use of insulin, %	**1.36 (1.09-1.69)**	**0.007**	1.12 (0.79-1.57)	0.530
LDL-C, mg/dL	1.00 (0.996-1.002)	0.521	1.00 (0.996-1.01)	0.510
eGFR, ml/min/1.73m^2	1.00 (0.995-1.01)	0.692	1.00 (0.99-1.01)	0.690
Albuminuria (A2 or above), %	0.93 (0.75-1.16)	0.518	1.01 (0.73-1.41)	0.940
Adiponectin†, ug/ml	**1.19 (1.05-1.35)**	**0.006**	**1.23 (1.03-1.47)**	**0.024**
hsCRP†, ug/ml	**1.07 (1.01-1.13)**	**0.024**	1.03 (0.95-1.13)	0.490

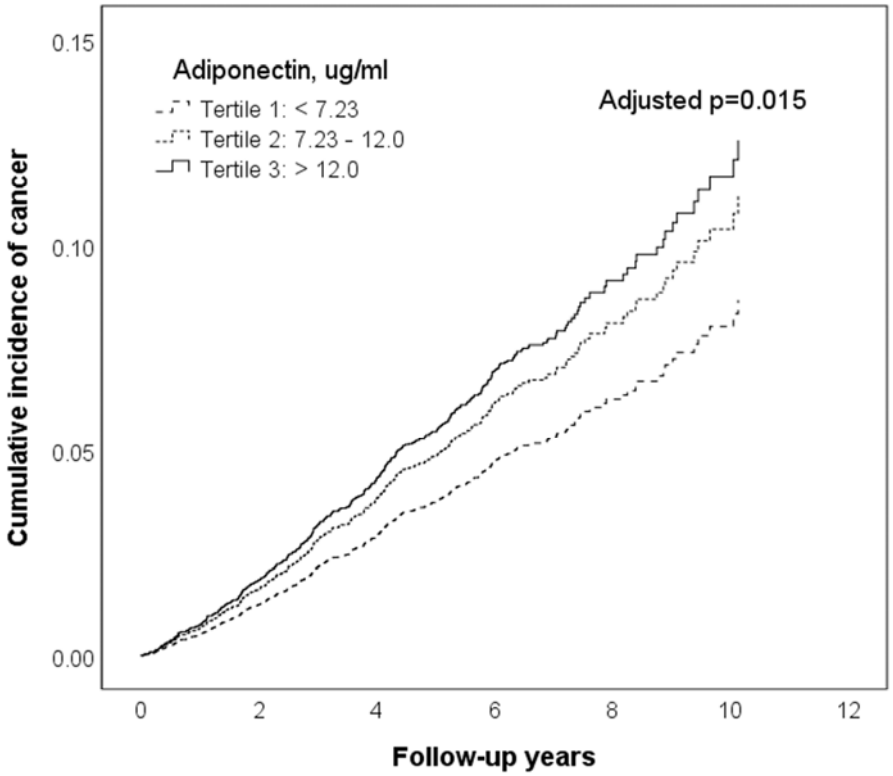
*Competing risk analysis was used; Values in **BOLD** were statistically significant.

†Log base 2-transformed before analysis; Hazard ratio for adiponectin referred to the respective risk per doubling of serum adiponectin concentration in ug/ml.

HR, hazard ratio; 95%CI, 95% confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol (LDL-C); hsCRP, high sensitive C-reactive protein.

Hypertension was defined as blood pressure ≥ 140 / 90 mmHg or on anti-hypertensive medications; Albuminuria category was classified according to urine albumin to creatinine ratio: A1 <30mg/g, A2 30-300 mg/g and A3 >300mg/g.

Figure 1 Cumulative incidence of cancer stratified by the tertiles of serum adiponectin concentrations of the study participants after multivariable adjustments



Other variables inlcuded in the multivariable cox regression model were sex, age, ever-smoking, body mass index, hypertension, history of cardiovascular disease, use of metformin, use of insulin, low density lipoprotein cholesterol, estimated glomerular filtration rate, albuminuria and high-sensitivity C-reactive protein