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Sex-specific associations between adiponectin and leptin signaling and pancreatic cancer survival

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Abstract

Background: Circulating adiponectin and leptin have been associated with risk of pancreatic cancer. However, the relationship between long-term exposure to these adipokines in the prediagnostic period with patient survival has not been investigated.

Methods: Adipokine levels were measured in prospectively collected samples from 472 pancreatic cancer patients. Due to sex-specific differences in adipokine levels, associations were evaluated separately for men and women. In a subset of 415 patients, we genotyped 23 nucleotide polymorphisms (SNPs) in adiponectin receptor genes (*ADIPOR1, ADIPOR2*) and 30 SNPs in the leptin receptor gene (*LEPR*).

Results: Adiponectin levels were inversely associated with survival in women (HR=1.47, 95% CI: 1.03–2.11, comparing top to bottom quartile) but not in men (HR=0.93, 95% CI: 0.54–1.59). The SNPs rs10753929 and rs1418445 in *ADIPOR1* were associated with survival in the combined population (per minor allele HR=0.66, 95% CI: 0.51–0.84, and HR=1.33, 95% CI: 1.12–1.58, respectively). Among SNPs in *LEPR,* rs12025906, rs3790431, and rs17127601 were associated with survival in the combined population [HRs (95% CI) of 1.54 (1.25–1.90), 0.72 (0.59–0.88), and 0.70 (0.56–0.89), respectively], while rs11585329 was associated with survival in men only (HR=0.39, 95% CI: 0.23–0.66) (P-interaction=0.0002).

Conclusions: High levels of adiponectin in the prediagnostic period were associated with shorter survival among women, but not among men with pancreatic cancer. Several polymorphisms in *ADIPOR1* and *LEPR* are associated with patient survival.

Impact: Our findings reveal the association between adipokine signaling and pancreatic cancer survival and demonstrate the importance of examining obesity-associated pathways in relation to pancreatic cancer in a sex-specific manner.

Keywords

pancreatic cancer; survival; obesity; adiponectin; leptin

Introduction

Pancreatic cancer is currently the third leading cause of cancer deaths in the United States, with a 5-year survival of 12%% (1). Obesity, defined as a body mass index (BMI) higher than 30 kg/m^2, has been associated with both increased risk and decreased survival of pancreatic cancer patients (2, 3).

Several mechanisms have been proposed for the role of obesity in pancreatic cancer, including altered levels of hormones secreted by adipose tissue (adipokines), elevated systemic inflammation, hyperinsulinemia, altered cholecystokinin signaling, and gut dysbiosis, but the pathways leading from obesity to increased risk and higher mortality from pancreatic cancer are not well understood (4, 5). Given that more than 40% of the U.S. population is obese (6) and the prevalence of obesity is expected to further increase, it is important to understand how the obesity-associated pathways drive pancreatic cancer progression.

Obese individuals have significant differences in plasma levels of adiponectin (7) and leptin (8), which are hormones primarily responsible for regulating energy balance and metabolism (9). However, by activating their respective receptors (ADIPOR1/ADIPOR2 and LEPR) that are expressed in pancreatic tumor tissue (10, 11), adiponectin and leptin also interact with several signaling pathways that regulate pancreatic tumor cell proliferation, angiogenesis and metastasis (5). We and others have previously shown an association of high leptin and low adiponectin levels with increased risk of pancreatic cancer (12–16). However, the association of these hormones in the prediagnostic period with patient survival has not been investigated.

To evaluate exposure to adipokine levels in the prediagnostic period in relation to patient survival, we measured circulating adiponectin and leptin levels in blood samples collected up to 26 years before diagnosis in 472 pancreatic cancer patients. In a subset of 415 patients, we also evaluated polymorphisms in genes coding for the adiponectin and leptin receptors in relation to patient survival.

Materials and Methods

Study population

This study included pancreatic cancer patients identified among participants from five prospective cohort studies: Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), Physicians' Health Study (PHS), Women's Health Initiative–Observational Study (WHI-OS), and Women's Health Study (WHS). HPFS was started in 1986, when 51,529 male U.S. based health professionals aged 40–75 completed a mailed biennial questionnaire (17). NHS is a prospective study of 121,700 female U.S. based nurses initiated in 1976, when nurses aged 30–55 returned a mailed questionnaire (18). In both HPFS and NHS, participants were followed by biennial questionnaires that collected demographic, lifestyle and medical history information. PHS is a clinical trial initiated in 1982 to study aspirin and β-carotene supplementation among 22,071 male physicians aged 40–84 years (19). The trial was completed in 1995 and participants were further followed as an observational cohort. WHI is an observational cohort study that enrolled 93,676 women aged 50–79 years from 1994 to 1998 (20). Participants were asked to return a completed baseline questionnaire and subsequent annual questionnaires. WHS is a randomized clinical trial of low-dose aspirin and vitamin E that enrolled 39,876 female health professionals aged 45 years or older between 1992 and 1995 (21). Following trial completion in 2004, 33,682 women continued being followed as an observational cohort. This study was conducted in accordance with recognized ethical guidelines and approved by the institutional review boards of Brigham and Women's Hospital (Boston, MA) and the Harvard T.H. Chan School of Public Health, and those of participating registries as required. All the participants provided written informed consent.

Pancreatic cancer cases were identified on self-administered questionnaires (returned annually in PHS, WHI and WHS, and biennially in NHS and HPFS), or through death records reporting pancreatic cancer as a cause of death (ICD code 157). All cases included in this analysis were confirmed by medical records, death certificates or cancer registry data that were reviewed by a physician blinded to exposure status. Deaths were identified from

next-of-kin, postal services, and the National Death Index, which captures >98% of deaths (22).

Blood collection and adipokine measurements

Blood samples were collected among 18,225 HPFS participants (1993–1995), 32,826 NHS participants (1989–1990), 14,916 PHS participants (1982–1984), 93,676 WHI participants (1994–1998), and 28,345 WHS participants (1992–1995). Details of blood collection, plasma processing and storage have been described previously (19, 20, 23–25).

We identified 492 pancreatic cancer patients with available plasma samples. Since pancreatic cancer patients often report weight loss in the months before pancreatic cancer diagnosis, which can itself lead to altered adipokine levels (26), we excluded 20 pancreatic cancer patients diagnosed within 1 year after blood collection, leading to the final dataset of 472 patients.

Plasma adiponectin and leptin were assayed in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA). Adiponectin was measured using an enzyme-linked immunosorbent assay (ELISA) from ALPCO Diagnostics (Salem, NH). Leptin was measured using ELISA with reagents from R&D Systems (Minneapolis, MN). All samples were handled identically in a single batch, and laboratory personnel was blinded to patient outcomes. The mean intra-assay coefficients of variance for quality control samples were <10% for both markers.

Single nucleotide polymorphism genotyping

A total of 29 SNPs in the *ADIPOR1*/*ADIPOR2* and 39 SNPs in *LEPR* genes (±20kb) were selected using Haploview tagger algorithm, with minor allele frequency (MAF) of ≥5% among Whites from the HapMap project database and using $r^2 \geq 0.8$. From 415 patients (Supplementary Table S1), DNA was extracted from buffy coat using QIAGEN QIAmp, and the amplification of genome was performed using GE Healthcare GenomiPhi. Genotyping was performed using a custom-designed Illumina Golden Gate assay at the Partners HealthCare Center for Personalized Genetic Medicine (Boston, MA). Seven SNPs in *LEPR* and 3 SNPs in *ADIPOR1/ADIPOR2* were not supported by the platform. In total, 2 SNPs in *LEPR* (rs913199, rs2148683) and 3 SNPs in *ADIPOR1/ ADIPOR2* (rs35916161, rs16850799, rs16928759) deviated from Hardy Weinberg equilibrium (P-value<0.05) and were thus removed from the analysis. In total, 23 SNPs in *ADIPOR1/ADIPOR2* and 30 SNPs in *LEPR* were analyzed (Supplementary Tables S2 and S3). Mean genotype concordance for replicate samples used for quality control was 98%.

Study variables

Information on participant characteristics including age, race/ethnicity, weight, height, physical activity, smoking status, and history of diabetes was obtained from the baseline questionnaire in PHS, WHI and WHS, and from the questionnaire preceding the blood draw in HPFS and NHS. Date of cancer diagnosis and cancer stage at diagnosis were obtained by medical records review as previously described (27).

Statistical analysis

Adiponectin and leptin levels differ significantly between men and women (28, 29). Furthermore, we and others have reported sex-specific associations between those adipokines and several health outcomes including diabetes, colorectal cancer and pancreatic cancer risk (12, 25, 30–32). We therefore investigated the association between adiponectin and leptin levels with pancreatic cancer survival separately for men and women.

Adiponectin and leptin levels were divided into sex-specific quartiles. To evaluate the association between adipokines and mortality in pancreatic cancer patients, we used multivariate Cox proportional hazards models using age as time scale and calculated hazard ratios (HRs) and 95% confidence intervals (CIs). Models were adjusted for study cohort, variables associated with adipokine levels [fasting time (<8 hours, ≥8 hours, missing), time between blood collection and diagnosis (continuous)], variables associated with pancreatic cancer survival [cancer stage (localized, locally advanced, metastatic, unknown) (1), year of diagnosis (continuous) (1)], and variables with prediagnostic levels or values associated with both adipokine levels and pancreatic cancer survival [race/ethnicity (White, Black, other, missing) (1), smoking (never, past, current with <25 cigarettes per day, current with ≥25 cigarettes per day, missing) (33)]. While the association between use of hormone replacement therapy (HRT) and pancreatic cancer survival in women has not been evaluated, we included this variable (categorized as premenopausal, postmenopausal HRT non-users, postmenopausal HRT users, unknown) in the multivariate models due to the impact of hormone therapy on metabolic (34) and immune systems (35) which could potentially be associated with pancreatic cancer survival. In the second multivariate model we also adjusted for BMI (continuous) and diabetes (yes, no) as those variables were previously associated with adipokine levels and pancreatic cancer survival (3, 36–38). We used the Wald test of the cross-term product between sex and adiponectin or leptin quartiles to evaluate the interaction between sex and adipokine levels. To further examine the linear association with continuous adipokine measurements and to evaluate the possibly non-linear association with pancreatic cancer risk, we used the likelihood ratio test comparing the model including linear and cubic spline terms with the model containing only linear term (39). To reduce the influence of extreme values, we excluded the patients with more than two standard deviations from the mean adiponectin or leptin measurements.

Proportional hazards assumption was verified by creating a time-dependent variable (product of adiponectin or leptin levels and time) and was satisfied for both adiponectin (women, P=0.16; men, P=0.14) and leptin (women, P=0.22; men, P=0.74).

Since adiponectin and leptin levels are moderately correlated (40, 41), we also considered a model adjusted for both markers. Linear trend across sex-specific quartiles was evaluated by entering quartile medians into models.

We performed stratified analysis by time between blood collection and diagnosis (1–10 years, ≥10 years), BMI (<30 kg/m^2, ≥30 kg/m^2), cancer stage (localized/locally advanced, metastatic), smoking status (never, ever), and HRT use among postmenopausal women (never, ever). Wald test of product of stratifying variable and marker levels was used to evaluate statistical significance of interaction.

The association between SNPs with patient survival was evaluated by using an additive model, where each genotype was modeled as number of copies of minor allele in a Cox proportional hazards model using age as time scale and adjusting for cohort, race/ethnicity, fasting time, smoking status, cancer stage, year of diagnosis, BMI, and diabetes. P-values adjusted for multiple hypotheses was calculated using Benjamini and Hochberg method (42). Analyses were performed using SAS 9.4 and R statistical software, and all the P-values were two-sided.

To explore the functional effect of evaluated SNPs on *LEPR* and *ADIPOR1/ADIPOR2* expression, we utilized the publicly available blood eQTLGen database (https://eqtlgen.org/cis-eqtls.html). This database was generated in 31,467 blood samples from 37 cohorts of the eQTLGen Consortium to identify regulatory mechanisms for genetic variants identified in genome-wide association studies (GWAS) (43). More specifically, we queried the *cis*-eQTL database, since SNPs located proximally (<1 megabase) from the gene of interest have a stronger effect on gene expression (44).

Data availability statement

Data are accessible through the established data sharing policies described at https://www.nurseshealthstudy.org/researchers (email: nhsaccess@channing.harvard.edu) for NHS, https://sites.sph.harvard.edu/hpfs/for-collaborators for HPFS, https://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=login for PHS, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001964.v1.p1 and http://whs.bwh.harvard.edu/ for WHS, and at https://www.whi.org/page/working-with-whi-data for WHI.

Results

Characteristics of pancreatic cancer patients included in this analysis are shown in Table 1. Average (standard deviation) age at diagnosis was 71.4 (8.1) years, and the average time between blood collection and cancer diagnosis was 8.2 (5.1) years. Most patients (69%) were women. Most patients were diagnosed with metastatic disease (44%), followed by locally advanced (24%), and localized disease (14%), while cancer stage was unknown for 85 (18%) patients. By the end of follow-up, 446 (94%) patients had died, and median overall survival was 6 months among all patients.

Consistent with previous studies (28, 29), women had higher mean levels of both leptin (27.3 ng/ml vs. 9.6 ng/ml in men) and adiponectin (8.7 μg/ml vs. 5.1 μg/ml in men). Patients with higher prediagnostic leptin had higher BMI, lower levels of physical activity, and were less likely to be White (Table 2). Conversely, patients with higher baseline adiponectin levels had lower BMI, higher levels of physical activity, and were more likely to be white (Table 3). After adjusting for age, study cohort and fasting status, leptin and adiponectin levels were inversely correlated (women: Spearman correlation coefficient =−0.32, P<0.001; men: Spearman correlation coefficient=−0.24, P<0.0001) (Supplementary Table S4), similar to previous reports (40, 41).

There was no significant association between leptin levels and survival among women (HR=1.22, 95% CI: 0.74–2.04, comparing top to bottom quartile), and no statistically

significant linear association (P-trend=0.11). Similar results were observed in the restricted cubic spline analysis (P-linear=0.09) (Supplementary Figure S1A). We observed no significant association between leptin and survival in men (HR=1.35, 95% CI: 0.54–3.33, comparing top to bottom quartile) (Table 4) (Supplementary Figure S1B). We observed no significant association between adiponectin levels with survival in men (HR=0.89, 95% CI: 0.46–1.70, comparing top to bottom quartile) (Supplementary Figure S2B). In women, we observed higher mortality in adiponectin quartile 2 (HR=1.46, 95% CI: 1.00–2.25), quartile 3 (HR=1.92, 95% CI: 1.27–2.92) and quartile 4 (HR=1.71, 95% CI: 1.15–2.54) compared to bottom quartile, with a statistically significant linear trend across quartiles (P-trend=0.03) (Table 4). Similar results were observed in the restricted cubic spline analysis (P-linear=0.05, Supplementary Figure S2A).

To account for correlation between adiponectin and leptin levels (Supplementary Table S4), we mutually adjusted for the two hormones in multivariate models and observed no change in associations. In men, there was no association with either adiponectin (HR=0.80, 95% CI: 0.41–1.57, comparing top to bottom quartile) or leptin levels (HR=01.48, 95% CI: 0.59–3.72) with survival. In women, we observed inverse association between adiponectin and mortality (HR=1.65, 95% CI: 1.11–2.47) and no association with leptin (HR=1.19, 95% CI: 0.71–2.00).

We next performed stratified analyses in women comparing top to bottom quartile of adiponectin levels. To evaluate whether higher adiponectin levels at the time of diagnosis were due to weight loss caused by the occult disease, we stratified the analysis by time between blood collection and cancer diagnosis. The association between adipokine levels and patient survival among women appeared stronger when blood was collected ≥10 years before diagnosis (HR=2.33, 95% CI: 0.65–8.34, comparing top to bottom quartile) compared to 1-<10 years before diagnosis (HR=1.47, 95% CI: 0.91–2.35, P-interaction=0.12) (Figure 1). Since smoking was previously reported as a modifier of the association between adiponectin and risk of pancreatic cancer (45), we performed a stratified analysis by smoking status at time of blood collection. We observed a significant association between adiponectin levels and survival among never smokers (HR=2.70, 95% CI: 1.30–5.63) and no association among ever smokers (HR=1.16, 95% CI: 0.63–2.13; P-interaction=0.02) (Figure 1). Since adiponectin levels are inversely correlated with BMI (7), we next examined the association separately by obesity status at the time of blood collection. We observed a significant association between adiponectin and survival in non-obese patients (HR=2.57, 95% CI: 1.57–4.21) but not in obese patients (HR=0.47, 95% CI: 0.10–2.21; P-interaction=0.003) (Figure 1).

Since the association between adiponectin and patient survival was observed only in women, to explore a potential role of sex hormones in adipokine signaling pathway, we performed stratified analyses by hormone replacement therapy (HRT) use among postmenopausal women. We observed no significant association between adiponectin levels and survival in never HRT users (HR=1.07, 95% CI: 0.43–2.70), and a significant association in ever HRT users (HR=1.79, 95% CI: 1.06–3.02, P-interaction=0.09) (Figure 1), suggesting an interaction between sex hormones and adiponectin levels on patient survival.

We next examined the association between polymorphisms in genes coding for the adiponectin receptors *ADIPOR1* and *ADIPOR2*. In women, two SNPs in *ADIPOR1* remained associated with patient survival after multiple hypotheses correction (Figure 2, Supplementary Table S2). We observed a positive association between rs1418445 and mortality (per minor allele HR=1.40, 95% CI: 1.15–1.71, adjusted P-value=0.02). We also observed an inverse association between rs10753929 and mortality in women (HR=0.67, 95% CI: 0.51–0.88, adjusted P=0.03). While the association between these two SNPs and survival did not reach statistical significance in men, the associations were relatively similar for both rs1418445 (HR=1.16, 95% CI: 0.78–1.74) and rs10753929 (HR= 0.71, 95% CI: 0.34–1.49), with no statistically significant interaction by sex (P=0.75 and 0.23, respectively). Interestingly, these SNPs have previously been associated with increased (rs1418445) or decreased (rs10753929) expression of *ADIPOR1* in the blood eQTL analysis (43) (Supplementary Table S5).

We next examined polymorphisms in *LEPR* in relation to patient survival. We observed a significant association between rs11585329 and survival in male (Figure 3, HR=0.39, 95% CI: 0.23–0.66, adjusted P=0.02) but not female patients (HR=1.04, 95% CI: 0.78–1.39, adjusted P=0.99), with a statistically significant interaction by sex (P=0.0002). Additionally, three SNPs were associated with survival in the combined population: rs12025906 (HR=1.54, 95% CI: 1.25–1.90, adjusted P<0.0001), rs3790431 (HR=0.72, 95% CI: 0.59–0.88, adjusted P=0.02), and rs17127601 (HR=0.70, 95% CI: 0.56–0.89, adjusted P=0.03), with similar estimates between men and women (Figure 3 and Supplementary Table S3) (all P-interaction > 0.2). Out of four SNPs in LEPR associated with survival, rs11585329 and rs12025906 were positively, and rs3790431 was negatively associated with *LEPR* expression in blood cells (Supplementary Table S5).

Discussion

In this large study of pancreatic cancer patients, higher adiponectin levels in the years preceding diagnosis were associated with increased mortality among women with pancreatic cancer. Furthermore, we observed associations between several single nucleotide polymorphisms within *ADIPOR1* and *LEPR* genes with survival of pancreatic cancer patients.

Higher circulating levels of leptin and lower circulating levels of adiponectin have previously been associated with increased risk of pancreatic cancer in several epidemiological studies (12–16). However, prior studies have not evaluated whether long-term exposure to these adipokines in the prediagnostic period is associated with survival of patients with pancreatic cancer. Since leptin and adiponectin interact with several pancreatic cancer-associated pathways potentially modifying the tumor microenvironment (5), we hypothesized that altered levels of those hormones in the period leading to diagnosis would not only be associated with the risk of pancreatic cancer, but also with tumor features and patient survival.

In this study, we observed an inverse association between circulating adiponectin and patient survival in women, but not in men. We also observed a statistically significant association

between survival of female patients and 2 polymorphisms affecting the expression of *ADIPOR1* in blood cells. While these SNPs were not associated with survival in men, the estimates were similar, and the lack of statistical significance may be due to a smaller sample size.

We and others have previously reported an inverse association between circulating adiponectin levels and pancreatic cancer incidence (13, 16). The positive association between adiponectin and mortality in the current study might therefore seem inconsistent. A similar pattern of associations was previously observed for colorectal cancer, where higher adiponectin levels were associated with lower risk and higher mortality of colorectal cancer patients (32, 46). In the context of pancreatic cancer, there are several potential explanations for the observed association.

Firstly, adiponectin levels are inversely correlated with weight (7), and higher adiponectin could be marking patients experiencing a more severe cancer-associated weight loss due to a more aggressive disease. However, patients diagnosed with pancreatic cancer within 1 year from blood collection were excluded from this analysis. Furthermore, the association between adiponectin levels and survival persisted when blood samples were analyzed from more than 10 years before diagnosis, when patients are unlikely to have occult weight loss due to pancreatic cancer. Individuals with higher adiponectin levels in prediagnostic period have a lower BMI and may therefore have lower skeletal muscle mass, which has been positively associated with patient survival (47–49). Another potential explanation for our observations is that higher adiponectin levels in the prediagnostic period alter the tumor microenvironment and contribute to development of more aggressive tumors. While adiponectin is generally considered an antitumorigenic hormone with a negative effect on tumor cell proliferation, metastasis and inflammation (50), studies have also shown a role of adiponectin in stimulating tumor angiogenesis (51) and blunting of antigen-specific T-cell responses (52). Alternatively, tumors developing in individuals with and despite high adiponectin levels might be different from those developing in low adiponectin individuals. For example, high adiponectin levels might be protective of more indolent tumors, but not of more aggressive tumors that ultimately lead to shorter patient survival. In our previously published study conducted in same patient population included in the current analysis, adiponectin levels >4.4 μg/ml were associated with decreased risk of pancreatic cancer (13). Interestingly, similar threshold for adiponectin levels was observed in this analysis, where patients with levels above ≥4.9 had shorter survival. It is therefore possible that high adiponectin levels indirectly lead to selection or enrichment of more aggressive tumors.

The association between adiponectin levels with pancreatic cancer survival was observed only in women. Epidemiological studies have previously reported sex-specific associations between adiponectin and several outcomes including diabetes (53) and metabolic syndrome (54, 55). There are several potential explanations for these differences. Similar to previous studies (29), adiponectin levels in our study were significantly higher in women than in men, and higher adiponectin levels might be required for activating potential pathways associated with shorter survival. However, we used the cutoff of adiponectin levels associated with survival in women (≥4.9 μg/ml) and observed no association with mortality in men. Alternatively, these sex-specific associations could be due to interaction between sex

hormones and adipokine signaling. In our study, the association between adiponectin levels and survival was limited to women using hormone replacement therapy, supporting this hypothesis. Sex hormones, more specifically estrogen interacts with adiponectin signaling on several levels. Estrogen alters expression of both adiponectin (56) and adiponectin receptors (57), and modulates the effect of adiponectin on proliferation and apoptosis of breast cancer cells (58). Lastly, the observed difference might be due to a smaller number of male compared to female patients.

In this study we observed an association between 4 polymorphisms in *LEPR* with patient survival. Furthermore, the association between rs11585329 and patient survival was observed only in men. We have previously reported sex-specific associations between leptin and *LEPR* polymorphisms and pancreatic cancer risk (12). In this study, higher leptin levels were associated with increased risk of pancreatic cancer in men, but not in women. We also reported an association between rs10493380 in *LEPR* and increased risk of pancreatic cancer in women (12). The results of the current analysis further strengthen the evidence that leptin signaling might be associated with pancreatic cancer in a sex-specific manner. Furthermore, the current analysis also suggests that the adiponectin and leptin pathways are associated not only with risk of developing pancreatic cancer, but also might be driving or selecting for tumors with different patient outcomes.

Strengths of the current study include a large number of pancreatic cancer patients with prospectively collected blood samples allowing the investigation of adiponectin signaling in the early stages of pancreatic tumor development. We were able to comprehensively evaluate several confounders associated with adiponectin levels and pancreatic cancer survival, most importantly BMI and diabetes (3, 37, 38, 59). Limitations of this study include adipokine measurements at a single time point before diagnosis. However, studies reported relatively stable leptin and adiponectin levels in healthy people. Repeated adiponectin and leptin measurements 1 year apart showed correlation coefficients of 0.85 and 0.74, respectively (60, 61). Our analysis includes a smaller number of male participants, and the observed lack of association in men could be due to limited statistical power. Next, we were not able to account for potential confounding by treatment type since this information was not available in our participants. However, it is unlikely that cancer treatments differ by circulating adiponectin levels measured in the years preceding diagnosis. The majority of participants in this study were White, and further studies are needed to validate adipokines in relation to survival of pancreatic cancer patients of different races and ethnicities.

In conclusion, higher adiponectin levels in the prediagnostic period and SNPs affecting expression of adiponectin receptor *ADIPOR1* were associated with shorter survival in women with pancreatic cancer. Further epidemiological and experimental studies are necessary to determine mechanisms behind the observed associations and to further elucidate the complex and sex-specific relationship between adiponectin and pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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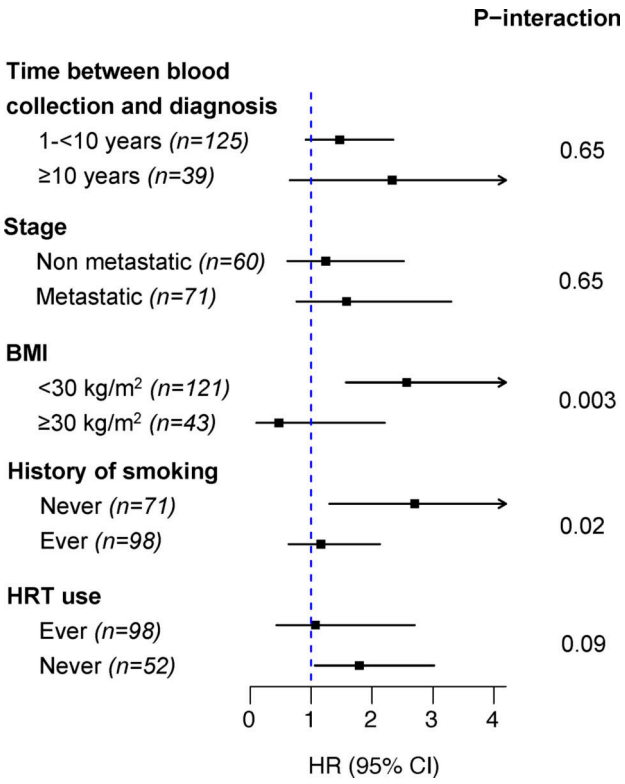

Figure 1.

[a]Hazard ratio (HR) and 95% confidence intervals (CI) of the association between top and bottom quartile of adiponectin estimated using a Cox proportional hazards model with age as time scale, adjusted for cohort (NHS, WHI, WHS), race (White, Black, other, missing), stage (localized, locally advanced, metastatic, unknown), year of diagnosis (continuous), fasting time (<8 hours, ≥8 hours, missing), smoking (never, past, current with <25 cigarettes per day, current with ≥25 cigarettes per day, missing), time between blood collection and diagnosis, HRT use (premenopausal, postmenopausal HRT non-users, postmenopausal HRT users, unknown), BMI (continuous) and diabetes (yes, no), with exception of stratifying covariate. P-interaction was calculated using the Wald test of product term of stratifying variable and adiponectin levels. Blue vertical line indicates no association.

[b]Among postmenopausal women

Abbreviations: HRT, hormone replacement therapy

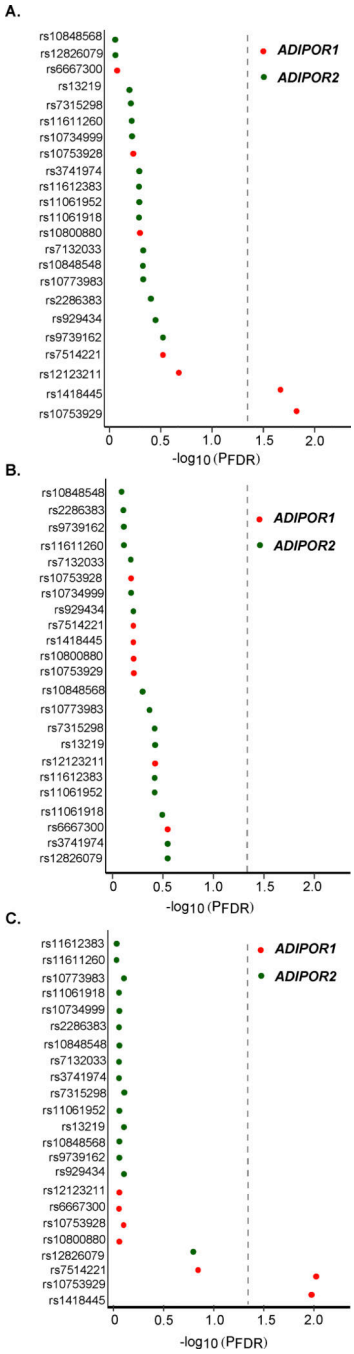

Figure 2.

P-values of the association between genetic polymorphisms in *ADIPOR1* (red dots) and *ADIPOR2* (green dots) and pancreatic cancer survival in A. women, B. men, and C. overall. Each SNP was modeled as number of minor allele copies in a Cox proportional hazards model using age as time scale, adjusted for cohort (women: NHS, WHI, WHS; men: HPFS, PHS), race (White, Black, other, missing), stage (localized, locally advanced, metastatic, unknown), year of diagnosis (continuous), fasting time (<8 hours, ≥8 hours, missing), smoking (never, past, current with <25 cigarettes per day, current with ≥25 cigarettes per

day, missing), time between blood collection and diagnosis, HRT use (in women only; premenopausal, postmenopausal HRT non-users, postmenopausal HRT users, unknown), BMI (continuous) and diabetes (yes, no). The gray dashed line indicates the statistical significance threshold after multiple hypotheses correction.

Abbreviations: HRT, hormone replacement therapy

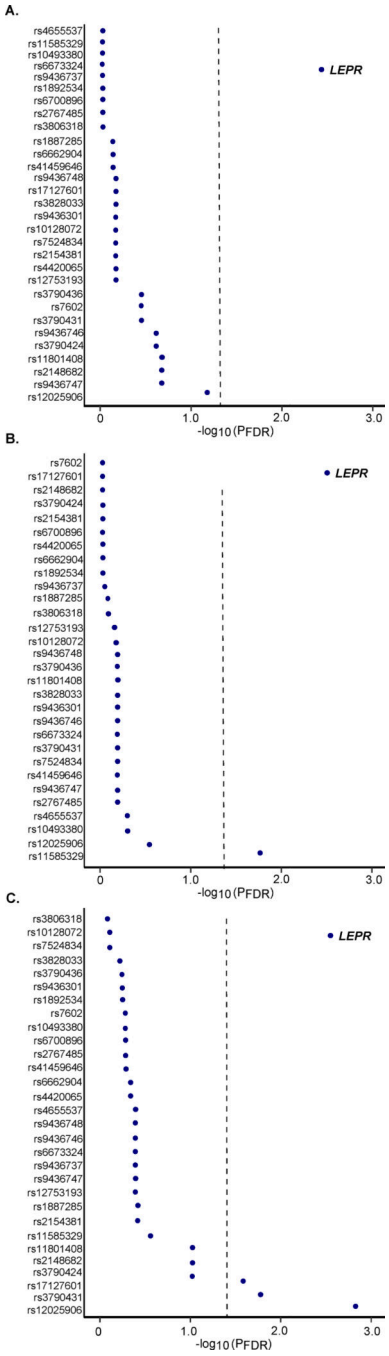

Figure 3.

P-values of the association between genetic polymorphisms in *LEPR* (blue dots) and pancreatic cancer survival in A. women, B. men, and C. overall population. Each SNP was modeled as number of minor allele copies in a Cox proportional hazards model using age as time scale, adjusted for cohort (women: NHS, WHI, WHS; men: HPFS, PHS), race (White, Black, other, missing), stage (localized, locally advanced, metastatic, unknown), year of diagnosis (continuous), fasting time (<8 hours, ≥8 hours, missing), smoking (never, past, current with <25 cigarettes per day, current with ≥25 cigarettes per day, missing),

time between blood collection and diagnosis, HRT use (in women only; premenopausal, postmenopausal HRT non-users, postmenopausal HRT users, unknown), BMI (continuous) and diabetes (yes, no). The gray dashed line indicates the statistical significance threshold after multiple hypotheses correction.

Abbreviations: HRT, hormone replacement therapy

Table 1.

Baseline characteristics of patients with pancreatic cancer

Characteristic[a]	Men	Women	Overall
N	144	328	472
Age at blood collection (years)	61.5 (9.4)	64.1 (7.9)	63.3 (8.4)
Age at diagnosis (years)	72.5 (8.9)	70.9 (7.8)	71.4 (8.1)
Time between blood draw and diagnosis (years)	11.0 (6.2)	7.0 (3.9)	8.2 (5.1)
BMI (kg/m^2)	25.6 (3.1)	26.8 (5.6)	26.4 (5.0)
Physical activity (MET-h/week)	24.8 (31.5)	14.3 (16.0)	17.5 (22.4)
Race			
White	120 (83)	298 (91)	418 (89)
Black	2 (1)	14 (4)	16 (3)
Other	1 (1)	13 (4)	14 (3)
Missing	21 (15)	3 (1)	24 (5)
Menopausal status	NA		NA
Premenopausal		12 (4)	
Postmenopausal		306 (93)	
Unknown		10 (3)	
Hormone replacement therapy use[b]	NA		NA
Never		112 (37)	
Ever		187 (61)	
Unknown		7 (2)	
Diabetes	6 (4)	20 (6)	26 (6)
Cohort			
HPFS	74 (51)	0 (0)	74 (16)
NHS	0 (0)	101 (31)	101 (21)
PHS	70 (49)	0 (0)	70 (15)
WHI	0 (0)	196 (60)	196 (41)
WHS	0 (0)	31 (9)	31 (7)
History of smoking			
Never	53 (37)	142 (43)	195 (41)
Past	70 (49)	140 (43)	210 (44)
Current	21 (15)	43 (13)	64 (14)
Unknown	0 (0)	3 (1)	3 (1)
Year of diagnosis			
1984–2000	82 (57)	169 (52)	251 (53)
2001–2009	62 (43)	159 (48)	221 (47)
Stage at diagnosis			
Localized	25 (17)	39 (12)	64 (14)
Locally advanced	24 (17)	91 (28)	115 (24)
Metastatic	62 (43)	146 (45)	208 (44)
Unknown	33 (23)	52 (16)	85 (18)

Characteristic[a]	Men	Women	Overall
Median (IQR) survival (months)			
Overall	5 (2–12)	6 (2–14)	6 (2–13)
By stage			
Localized	14 (7–24)	18 (5–45)	17 (7–31)
Locally advanced	10 (5–15)	11 (6–17)	10 (6–16)
Metastatic	3 (1–6)	3 (1–7)	3 (1–7)
Unknown	5 (1–9)	6 (2–11)	6 (2–11)

[a] Ascertained at time of blood collection, unless otherwise noted. Continuous variables are shown as mean (standard deviation), and categorical variables as number (percent), unless noted otherwise.

[b] Among postmenopausal women

Table 2.

Baseline patient characteristics by circulating leptin levels

	Leptin quartiles[b]			
Characteristic[a]	**1**	**2**	**3**	**4**
Women				
N cases	82	82	82	82
Age at blood draw (years)	64.1 (8.1)	64.2 (8.6)	63.8 (7.7)	64.4 (7.3)
Age at diagnosis (years)	71.2 (7.6)	71.2 (8.2)	70.5 (7.4)	70.6 (7.9)
Time between blood draw and diagnosis (years)	7.3 (3.8)	7.3 (4.2)	7.1 (4.0)	6.4 (3.7)
BMI (kg/m^2)	22.3 (3.5)	24.8 (2.7)	28.5 (6.1)	31.6 (5.1)
Physical activity (MET-h/week)	19.8 (19.0)	13.9 (13.5)	14.1 (16.0)	9.4 (13.2)
White race	77 (94)	74 (90)	74 (90)	73 (89)
Diabetes	2 (2)	6 (7)	7 (9)	5 (6)
Cohort				
NHS	31 (38)	28 (34)	23 (28)	19 (23)
WHI	43 (52)	47 (57)	50 (61)	56 (68)
WHS	8 (10)	7 (9)	9 (11)	7 (9)
History of smoking				
Never	37 (45)	34 (41)	37 (45)	34 (41)
Past	34 (41)	33 (40)	30 (37)	43 (52)
Current	10 (12)	14 (17)	14 (17)	5 (6)
Unknown	1 (1)	1 (1)	1 (1)	0 (0)
Menopausal status				
Premenopausal	4 (5)	3 (4)	2 (2)	3 (4)
Postmenopausal	75 (91)	75 (91)	78 (95)	78 (95)
Unknown	3 (4)	4 (5)	2 (2)	1 (1)
Hormone replacement therapy use[c]				
Never	28 (37)	22 (29)	32 (41)	30 (38)
Ever	47 (63)	50 (67)	43 (55)	47 (60)
Unknown	0 (0)	3 (4)	3 (4)	1 (1)
Year of diagnosis				
1984–2000	46 (56)	40 (49)	37 (45)	46 (56)
2001–2009	36 (44)	42 (51)	45 (55)	36 (44)
Stage at diagnosis				
Localized	11 (13)	10 (12)	11 (13)	7 (9)
Locally advanced	23 (28)	24 (29)	22 (27)	22 (27)
Metastatic	34 (41)	37 (45)	39 (48)	36 (44)
Unknown	14 (17)	11 (13)	10 (12)	17 (21)
Men				
N cases	36	36	36	36
Age at blood draw (years)	60.5 (9.0)	60.4 (10.3)	60.8 (9.4)	64.2 (8.5)
Age at diagnosis (years)	72.3 (9.2)	72.7 (7.9)	70.9 (10.2)	74.0 (8.2)

Characteristic[a]	Leptin quartiles[b]			
	1	2	3	4
Time between blood draw and diagnosis (years)	11.8 (6.7)	12.3 (6.3)	10.1 (6.0)	9.8 (5.8)
BMI (kg/m^2)	23.6 (1.5)	24.6 (1.8)	25.6 (2.2)	28.7 (3.7)
Physical activity (MET-h/week)	30.4 (40.7)	25.6 (30.2)	21.1 (27.9)	21.9 (25.7)
White race	31 (86)	32 (89)	26 (72)	21 (86)
Diabetes	2 (6)	0 (0)	1 (3)	3 (8)
Cohort				
HPFS	19 (53)	17 (47)	17 (47)	21 (58)
PHS	17 (47)	19 (53)	19 (53)	15 (42)
History of smoking				
Never	14 (39)	16 (44)	12 (33)	11 (31)
Past	17 (47)	14 (39)	19 (53)	20 (56)
Current	5 (14)	6 (17)	5 (14)	5 (14)
Year of diagnosis				
1984–2000	16 (44)	15 (42)	25 (69)	26 (72)
2001–2009	20 (56)	21 (58)	11 (31)	10 (28)
Stage at diagnosis				
Localized	10 (28)	5 (14)	8 (22)	2 (6)
Locally advanced	5 (14)	5 (14)	7 (19)	7 (19)
Metastatic	12 (33)	17 (47)	16 (44)	17 (47)
Unknown	9 (25)	9 (25)	5 (14)	10 (28)

[a] Ascertained at time of blood collection, unless otherwise noted. Continuous variables are shown as mean (standard deviation), and categorical variables as number (percent), unless noted otherwise.

[b] Sex-specific quartiles

[c] Among postmenopausal women

Table 3.

Baseline patient characteristics by circulating adiponectin levels

	Adiponectin quartiles[b]			
Characteristic[a]	**1**	**2**	**3**	**4**
Women				
N cases	82	82	82	82
Age at blood draw (years)	62.2 (8.6)	63.2 (7.7)	65.6 (8.0)	65.6 (6.7)
Age at diagnosis (years)	69.1 (8.2)	69.2 (8.0)	72.3 (7.5)	72.9 (6.6)
Time between blood draw and diagnosis (years)	7.0 (4.0)	6.3 (4.1)	7.0 (3.7)	7.7 (3.9)
BMI (kg/m^2)	29.2 (6.4)	27.0 (5.0)	26.5 (5.5)	24.3 (4.3)
Physical activity (MET-h/week)	14.3 (15.5)	11.3 (12.5)	15.1 (16.0)	16.6 (19.0)
White race	70 (85)	76 (93)	74 (90)	78 (95)
Diabetes	7 (9)	4 (5)	5 (6)	4 (5)
Cohort				
NHS	27 (33)	27 (33)	22 (27)	25 (30)
WHI	45 (55)	46 (56)	54 (66)	51 (62)
WHS	10 (12)	9 (11)	6 (7)	6 (7)
History of smoking				
Never	38 (46)	38 (46)	33 (40)	33 (40)
Past	32 (39)	31 (38)	36 (44)	41 (50)
Current	11 (13)	13 (16)	12 (15)	7 (9)
Unknown	1 (1)	0 (0)	1 (1)	1 (1)
Menopausal status				
Premenopausal	4 (5)	4 (5)	4 (5)	0 (0)
Postmenopausal	73 (89)	75 (91)	77 (94)	81 (99)
Unknown	5 (6)	3 (4)	1 (1)	1 (1)
Hormone replacement therapy use[c]				
Never	25 (34)	31 (41)	29 (38)	27 (33)
Ever	46 (63)	42 (56)	47 (61)	52 (64)
Unknown	2 (3)	2 (3)	1 (1)	2 (2)
Year of diagnosis				
1984–2000	43 (52)	51 (62)	40 (49)	35 (43)
2001–2009	39 (48)	31 (38)	42 (51)	47 (57)
Stage at diagnosis				
Localized	5 (6)	8 (10)	14 (17)	12 (15)
Locally advanced	25 (30)	22 (27)	26 (32)	18 (22)
Metastatic	38 (46)	40 (49)	35 (43)	33 (40)
Unknown	14 (17)	12 (15)	7 (9)	19 (23)
Men				
N cases	35	36	36	36
Age at blood draw (years)	61.0 (9.0)	60.7 (8.9)	61.6 (8.9)	62.7 (10.8)
Age at diagnosis (years)	71.6 (8.3)	72.7 (8.6)	72.0 (9.2)	73.8 (9.5)

Characteristic[a]	Adiponectin quartiles[b]			
	1	2	3	4
Time between blood draw and diagnosis (years)	10.6 (5.3)	12.0 (6.1)	10.4 (6.5)	11.1 (7.0)
BMI (kg/m^2)	27.0 (3.3)	25.6 (2.6)	26.0 (3.4)	24.2 (2.3)
Physical activity (MET-h/week)	19.9 (27.5)	30.7 (40.4)	22.0 (20.5)	27.0 (34.4)
White race	28 (80)	30 (83)	30 (83)	31 (86)
Diabetes	2 (6)	3 (8)	0 (0)	1 (3)
Cohort				
HPFS	19 (54)	15 (42)	21 (58)	18 (50)
PHS	16 (46)	21 (58)	15 (42)	18 (50)
History of smoking				
Never	13 (37)	14 (39)	17 (47)	9 (25)
Past	16 (46)	18 (50)	17 (47)	19 (53)
Current	6 (17)	4 (11)	2 (6)	8 (22)
Year of diagnosis				
1984–2000	22 (63)	20 (56)	19 (53)	20 (56)
2001–2009	13 (37)	16 (44)	17 (47)	16 (44)
Stage at diagnosis				
Localized	9 (26)	6 (17)	3 (8)	7 (19)
Locally advanced	7 (20)	5 (14)	9 (25)	3 (8)
Metastatic	10 (29)	18 (50)	15 (42)	18 (50)
Unknown	9 (26)	7 (19)	9 (25)	8 (22)

[a] Ascertained at time of blood collection, unless otherwise noted. Continuous variables are shown as mean (standard deviation), and categorical variables as number (percent), unless noted otherwise.

[b] Sex-specific quartiles

[c] Among postmenopausal women

Table 4.

Prediagnostic circulating adipokine levels and survival of patients with pancreatic cancer

	Q1	Q2	Q3	Q4	P-trend[c]	P-interaction[d]
LEPTIN						
Women						
Leptin (ng/ml)	<11.9	11.9–21.4	21.5–38.2	>38.3		
Deaths/cases	76/82	77/82	74/82	77/82		
Model I[a], HR (95% CI)	1 (Ref)	0.78 (0.54–1.13)	1.02 (0.70–1.49)	1.35 (0.92–1.97)	0.02	
Model II[b], HR (95% CI)	1 (Ref)	0.72 (0.49–1.06)	0.94 (0.61–1.45)	1.22 (0.74–2.04)	0.11	
Men						
Leptin (ng/ml)	<4.4	4.6–7.3	7.3–13.9	>14.4		
Deaths/cases	34/36	36/36	36/36	36/36		
Model I[a], HR (95% CI)	1 (Ref)	1.35 (0.75–2.43)	1.21 (0.63–2.31)	1.21 (0.64–2.30)	0.08	
Model II[b], HR (95% CI)	1 (Ref)	1.37 (0.76–2.49)	1.25 (0.64–2.47)	1.35 (0.54–3.33)	0.66	
Overall						
Deaths/cases	110/118	113/118	110/118	113/118		
Model I[a], HR (95% CI)	1 (Ref)	0.84 (0.63–1.20)	0.95 (0.71–1.28)	1.27 (0.94–1.72)	0.01	0.59
Model II[b], HR (95% CI)	1 (Ref)	0.80 (0.60–1.07)	0.87 (0.63–1.20)	1.09 (0.74–1.60)	0.18	0.79
ADIPONECTIN						
Women						
Adiponectin (μg/ml)	<4.8	4.9–7.4	7.4–11.0	>11.1		
Deaths/cases	74/82	77/82	75/82	78/82		
Model I[a], HR (95% CI)	1 (Ref)	1.46 (1.00–2.15)	1.92 (1.27–2.92)	1.57 (1.07–2.32)	0.07	
Model II[b], HR (95% CI)	1 (Ref)	1.49 (1.01–2.19)	2.01 (1.32–3.06)	1.71 (1.15–2.54)	0.03	
Men						
Adiponectin (μg/ml)	<3.1	3.1–4.5	4.6–6.2	>6.5		
Deaths/cases	35/35	36/36	36/36	34/36		
Model I[a], HR (95% CI)	1 (Ref)	1.16 (0.62–2.19)	1.43 (0.72–2.83)	0.85 (0.45–1.60)	0.54	
Model II[b], HR (95% CI)	1 (Ref)	1.21 (0.64–2.30)	1.52 (0.78–3.02)	0.89 (0.46–1.70)	0.52	
Overall						
Deaths/cases	109/117	113/118	111/118	112/118		
Model I[a], HR (95% CI)	1 (Ref)	1.19 (0.88–1.60)	1.51 (1.11–2.05)	1.21 (0.90–1.63)	0.12	0.08
Model II[b], HR (95% CI)	1 (Ref)	1.21 (0.89–1.63)	1.58 (1.16–2.15)	1.30 (0.96–1.78)	0.04	0.06

[a]Cox proportional hazards model using age as time scale, adjusted for cohort (women: NHS, WHI, WHS; men: HPFS, PHS), race (White, Black, other, missing), stage (localized, locally advanced, metastatic, unknown), year of diagnosis (continuous), fasting time (<8 hours, ≥8 hours, missing), smoking (never, past, current with <25 cigarettes per day, current with ≥25 cigarettes per day, missing), time between blood collection and diagnosis, and HRT use (in women only; premenopausal, postmenopausal HRT non-users, postmenopausal HRT users, unknown)

[b]Additionally adjusted for BMI (continuous) and diabetes (yes, no)

[c]Wald test of sex-specific quartile medians as a continuous variable

[d] Wald test of the cross-term product between sex and adiponectin or leptin quartiles