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Prediagnostic Leukocyte Telomere Length and Pancreatic Cancer Survival

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Abstract

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Background: Leukocyte telomere length has been associated with risk of subsequent pancreatic cancer. Few prospective studies have evaluated the association of prediagnostic leukocyte telomere length with pancreatic cancer survival.

Methods: We prospectively examined the association of prediagnostic leukocyte telomere length with overall survival (OS) time among 423 participants diagnosed with pancreatic adenocarcinoma between 1984 and 2008 within the Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, and Women's Health Initiative. We measured prediagnostic leukocyte telomere length in banked blood samples using quantitative polymerase chain reaction. Cox proportional hazards models were used to estimate hazard ratios (HRs) for OS with adjustment for potential confounders. We also evaluated 10 single nucleotide polymorphisms (SNPs) at the *TERT* (telomerase reverse transcriptase) locus.

Results: Shorter prediagnostic leukocyte telomere length was associated with reduced OS among patients with pancreatic cancer ($P_{\text{trend}} = 0.04$). The multivariable-adjusted HR for OS comparing the lowest to highest quintiles of leukocyte telomere length was 1.39 (95% confidence interval, 1.01–1.93), corresponding to a 3-month difference in median OS time. In an analysis excluding cases with blood collected within two years of cancer diagnosis, the association was moderately stronger (HR, 1.55; 95% confidence interval, 1.09–2.21; comparing the lowest to highest quintiles; $P_{\text{trend}} = 0.01$). No prognostic association or effect modification for the prognostic association of prediagnostic leukocyte telomere length was noted in relation to the studied SNPs.

Conclusions: Prediagnostic leukocyte telomere length was associated with pancreatic cancer survival.

Impact: Prediagnostic leukocyte telomere length can be a prognostic biomarker in pancreatic cancer.

Keywords

biomarkers; epidemiology; pancreatic neoplasms; survival analysis; telomere shortening

Introduction

Pancreatic cancer currently represents the third leading cause of cancer-related death in the United States (1). Despite increased efficacy of newer chemotherapy programs (2–4), patient prognosis remains poor with short survival times and an overall 5-year survival rate of < 10% (1). A better understanding of prognostic factors may help develop novel therapeutic approaches to improve survival of patients with pancreatic cancer.

Telomeres are tandem repeats of TTAGGG nucleotides located at the ends of linear chromosomes, which are essential to maintain genome stability during cell division (5). Highly-shortened telomeres can cause chromosomal instability, and lead to cell immortalization and accumulation of genetic aberrations potentially contributing to carcinogenesis (5–7). Telomere shortening occurs early in pancreatic carcinogenesis (8–10). Telomerase reverse transcriptase is the catalytic subunit of telomerase, which plays a key role in maintaining telomere length, and genetic variants at the *TERT* (telomerase reverse transcriptase) locus are associated with pancreatic cancer risk (11–14).

Leukocyte telomere shortening may not only represent shortening of telomeres in the entire body, but also serve as a surrogate for long-term exposure to cancer risk factors including smoking, diabetes mellitus, and adiposity (15, 16). Epidemiological studies suggest that prediagnostic leukocyte telomere length is associated with risk of various cancer types including pancreatic ductal adenocarcinoma (11, 16, 17). Further evidence points to impaired maintenance of leukocyte telomeres as a prognostic factor for cancer progression after diagnosis (18–21). While recent studies support an association between shorter leukocyte telomere length and poorer survival among cancer patients overall (22, 23), the prognostic associations observed were inconsistent across studies, and only a small number of patients with pancreatic cancer have been evaluated.

To test the hypothesis that prediagnostic leukocyte telomere length might be associated with survival among patients with pancreatic ductal adenocarcinoma, we conducted a large prospective study using four U.S. cohorts that included banked blood samples and detailed information on lifestyle and clinical factors. We further examined single nucleotide polymorphisms (SNPs) at the *TERT* locus that have been associated with risk of multiple cancers (24) and their interactions with prediagnostic leukocyte telomere length, in relation to survival among patients with pancreatic cancer.

Materials and Methods

Study population

We evaluated pancreatic cancer cases from four U.S. prospective cohort studies: Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), Physicians' Health Study (PHS), and Women's Health Initiative (WHI) (25, 26). The HPFS enrolled 51,529 male health professionals aged 40–75 years in 1986 (27–29). The NHS enrolled 121,700 female nurses aged 30–55 years in 1976 (28–30). The PHS is a randomized clinical trial of aspirin and β -carotene that enrolled 22,071 male physicians aged 40–84 years in 1982 (31). After completion of the randomized components in 1995, study participants have been followed as an observational cohort. The WHI Observational Study enrolled 93,676 postmenopausal women aged 50–79 years between 1994 and 1998 (32). In all studies, participants have completed regular mailed questionnaires (25, 26). Written informed consent was obtained from all participants in each cohort. This study was conducted in accordance with the Declaration of Helsinki, and after approval by the Human Research Committee at Brigham and Women's Hospital (Boston, MA).

We included 423 patients diagnosed with pancreatic cancer between 1984 and 2008 with available prediagnostic blood samples (Table 1). As previously described (25, 26), incident pancreatic cancer cases were identified by self-report or during follow-up of participants' deaths. Physicians blinded to exposure status confirmed the diagnosis of pancreatic cancer by review of medical records, death certificates, or cancer registry data. Deaths were ascertained from next of kin, the U.S. postal service, or the National Death Index; this method has been shown to capture > 98% of deaths (33). Exclusion criteria included patients with non-adenocarcinoma histology or lack of available survival data.

Data collection

As previously described (25, 26), clinical data were collected from the prospective cohort studies. Information on demographics, lifestyle habits, and medical history was obtained from questionnaires preceding blood collection in HPFS and NHS, and from baseline questionnaires at enrollment (coinciding with blood collection) in PHS and WHI. In all cohorts, data were available for age at blood collection, sex, race/ethnicity, smoking status, body mass index (BMI), physical activity, and history of diabetes mellitus. Date of pancreatic cancer diagnosis and stage at diagnosis were determined through physician review of medical records. Cancer stage was classified as: localized (amenable to surgical resection); locally advanced (unresectable due to extrapancreatic extension but no distant metastases); or metastatic.

Measurement of leukocyte telomere length

As previously described (25, 26), blood samples were collected from 18,225 men in HPFS from 1993 to 1995, 32,826 women in NHS from 1989 to 1990, 14,916 men in PHS from 1982 to 1984, and 93,676 women in WHI from 1994 to 1998. All blood samples have been stored in well-monitored freezers. Procedures for collection, transportation, and storage of blood samples in these cohorts have been detailed elsewhere (34).

As previously described (11, 35), relative leukocyte telomere length was measured by a quantitative real-time polymerase chain reaction (PCR)-based assay. Genomic DNA was extracted from peripheral leukocytes using QIAamp 96 DNA Blood Kit (Qiagen, Chatsworth, CA), and was quantified using the PicoGreen reagent and 96-well spectrophotometer (Molecular Devices, Sunnyvale, CA). The ratio of telomere repeat copy number to a single-gene copy number (T/S ratio) was assayed in triplicate using a modified high-throughput quantitative PCR assay (7900HT Sequence Detection System; Applied Biosystems, Foster City, CA) (35, 36). Relative telomere length was calculated as exponentiated T/S ratio corrected for a reference sample. Coefficients of variation (CVs) within triplicates of telomere and single-gene assays were 0.6% and 0.5%, respectively, and CVs for the exponentiated T/S ratio were 12.9% (11).

Selection and genotyping of SNPs at the *TERT* locus

As previously described (11), we genotyped four SNPs at the *TERT* gene locus which were associated with cancer risk: rs401681 (pancreatic cancer) (14), rs402710 (lung cancer) (37), rs2736100 (lung cancer and glioma) (37, 38), and rs2853676 (glioma) (38). DNA was extracted from pooled blood samples as described above, and whole genome amplification was carried out using the Genomiphi kit (GE Healthcare, Boston, MA). All genotyping was performed using a custom-designed Illumina Golden Gate genotyping assay at Partners HealthCare Center for Personalized Genetic Medicine (Cambridge, MA). Replicate samples included for quality control ($n = 44$) had mean genotype concordance of 97.2% across the four SNPs (11). No SNP deviated from the Hardy-Weinberg equilibrium at $P < 0.01$. As previously described (11), we additionally obtained data on six independent risk loci at the *TERT* locus (rs451360, rs2736098, rs2853677, rs7726159, rs10069690, and rs13172201) (24) for 320 pancreatic cancer cases which were included in recent genome-wide association

studies of pancreatic cancer (PanScan studies) (13, 14). Genotyping and imputation methods in the PanScan studies were described previously (13).

Statistical analysis

We examined the association between prediagnostic leukocyte telomere length and overall survival among patients with pancreatic cancer. Telomeres shorten biologically with increasing age, and thus, age-adjusted leukocyte telomere length was computed by subtracting the predicted telomere length from the observed telomere length for each patient with pancreatic cancer (39–41). Considering potential alterations in leukocyte telomere length preceding pancreatic cancer diagnosis (11, 16, 17), we computed age-adjusted leukocyte telomere length for pancreatic cancer cases based on leukocyte telomere length among cancer-free individuals. In our previous nested case-control study (11), we randomly selected up to three controls for each pancreatic cancer case, matching on year of birth, prospective cohort (also matched on sex), smoking status, fasting status at blood collection, and month/year of blood collection. Using 936 controls matched to the current study population of 423 cases, we conducted a linear regression on leukocyte telomere length according to age at blood collection, and used the coefficients to calculate predicted leukocyte telomere length for patients with pancreatic cancer. We defined quintiles of age-adjusted prediagnostic leukocyte telomere length among all patients with pancreatic cancer. Overall survival time was calculated as time from pancreatic cancer diagnosis to death or last follow-up, whichever came first.

In our primary analyses, we pooled data from the four cohort studies and used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for overall mortality by quintiles of age-adjusted leukocyte telomere length before pancreatic cancer diagnosis. Tests for trend were conducted by entering quintile-specific median values as a continuous variable in Cox regression models and evaluating the Wald test. The multivariable Cox regression models were adjusted for age at diagnosis (continuous), cohort (HPFS, NHS, PHS, or WHI; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown) (42), BMI (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²) (43), diabetes status (yes or no) (44), and cancer stage (localized, locally advanced, metastatic, or unknown). Subsequently, we further adjusted for time from blood collection to cancer diagnosis (< 5, 5–10, or ≥ 10 years). We examined a possible non-linear association between prediagnostic leukocyte telomere length and pancreatic cancer survival using restricted cubic splines (45). The assumption of proportionality of hazards was satisfied by evaluating a time-dependent covariate, which was the cross-product of quintile-specific median values of prediagnostic leukocyte telomere length (continuous) and survival time ($P = 0.69$). We estimated median overall survival time and survival curves adjusted for covariates by using direct adjusted survival estimation (46, 47). This method uses the Cox regression model to estimate survival probabilities at each time-point for each individual and then averages them to obtain an overall survival estimate. We examined the heterogeneity in the association of prediagnostic leukocyte telomere length with pancreatic cancer survival between the cohorts using Cochran's Q statistic (48). We computed a pooled HR for overall mortality by a standard deviation-decrease in prediagnostic leukocyte telomere length using the

DerSimonian and Laird random-effects model (49). As exploratory analyses, we assessed whether the association of prediagnostic leukocyte telomere length with pancreatic cancer survival differed by time between measurements of leukocyte telomere length and cancer diagnosis. We also performed analyses stratified by sex, smoking status, BMI, cancer stage at diagnosis, and SNPs at the *TERT* locus associated with leukocyte telomere length (11, 50, 51). We assessed statistical interaction by entering main effect terms and the cross-product of leukocyte telomere length quartiles and a stratification variable into the model and evaluating likelihood ratio test. Given limited numbers of patients in strata of covariates of interest, we used quartiles of prediagnostic leukocyte telomere length in stratified analyses. As exploratory analyses, we examined the association of SNPs at the *TERT* locus with patient survival by entering each 3-level genotype as a continuous variable into multivariable-adjusted Cox regression model (additive model).

Two-sided P values < 0.05 were considered statistically significant in all analyses. All statistical analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

Results

Characteristics of 423 patients diagnosed with incident pancreatic ductal adenocarcinoma overall and by cohort are summarized in Table 1 and Supplementary Table S1, respectively. The median time from blood collection to pancreatic cancer diagnosis was 6.1 years. Prediagnostic leukocyte telomere length was inversely associated with age at blood collection (Spearman $r = -0.14$, $P = 0.004$). Among patients with available data on cancer stage ($n = 350$), 15.1%, 29.4%, and 55.5% of patients had localized, locally advanced, and metastatic disease, respectively. Prediagnostic leukocyte telomere length was not associated with cancer stage at diagnosis (Supplementary Table S2). In the combined cohort, median adjusted survival time was 16, 10, and 4 months for localized, locally advanced, and metastatic disease, respectively. At the end of follow-up, 401 pancreatic cancer cases (94.8% of combined cohort) were deceased.

Shorter prediagnostic leukocyte telomere length was associated with reduced survival time of pancreatic cancer patients ($P_{\text{trend}} = 0.04$, Table 2 and Fig. 1). The patients in the lowest vs. highest quintiles had a HR for overall mortality of 1.39 (95% CI, 1.01–1.93), corresponding to a 3-month shorter median survival. In the multivariable model further adjusted for time from blood collection to cancer diagnosis, our findings remained largely unchanged (Table 2). We fitted a restricted cubic spline curve for prediagnostic leukocyte telomere length in relation to pancreatic cancer survival, which did not suggest a non-linear association ($P_{\text{non-linearity}} = 0.59$). Taking into account the possible influence of subclinical malignancy on leukocyte telomere length, we conducted a sensitivity analysis excluding patients who were diagnosed with pancreatic cancer within two years of blood collection, which yielded a modestly stronger association between prediagnostic leukocyte telomere length and patient survival ($P_{\text{trend}} = 0.01$; Supplementary Table S3). We did not observe significant heterogeneity in the prognostic association of prediagnostic leukocyte telomere length between patients in the four cohorts ($P_{\text{heterogeneity}} = 0.95$, Fig. 2).

In exploratory analyses, we examined the temporal association of prediagnostic leukocyte telomere length with pancreatic cancer survival (Table 3). The association was stronger in patients whose blood samples were collected ≥ 6.1 years (median) before cancer diagnosis ($P_{\text{trend}} = 0.03$); in these patients, the HR for overall mortality comparing extreme quartiles of leukocyte telomere length was 1.60 (95% CI, 1.02–2.50).

In stratified analyses, we observed no statistically significant effect modification for the prognostic association of prediagnostic leukocyte telomere length by sex, smoking status, BMI, or cancer stage (all $P_{\text{interaction}} > 0.25$, Table 4).

In additional exploratory analyses, we examined patient survival in relation to 10 SNPs at the *TERT* gene locus. We observed no association of those SNPs with patient survival (all $P > 0.15$, Supplementary Table S4). We observed no statistically significant effect modification for the prognostic association of prediagnostic leukocyte telomere length by three SNPs at the *TERT* locus associated with leukocyte telomere length ($P_{\text{interaction}} > 0.36$, Supplementary Table S5).

Discussion

In the current pooled study conducted within four U.S. prospective cohorts, we found that shorter leukocyte telomere length before diagnosis of pancreatic cancer was associated with reduced patient survival. Specifically, patients with the shortest prediagnostic leukocyte telomere length had a 3-month reduction in median survival. Interestingly, leukocyte telomere length appeared to be more strongly associated with survival among patients with pancreatic cancer when measured more than six years before cancer diagnosis. Our findings raise the possibility that long-term impaired telomere maintenance preceding pancreatic cancer diagnosis may affect patient overall survival.

Evidence suggests that leukocyte telomere length may be associated with survival among cancer patients (22, 23), but data on pancreatic cancer are limited. In a Danish prospective cohort study involving 47,102 participants, prediagnostic leukocyte telomere length was not associated with survival among 124 patients with pancreatic cancer (HR for a 1-kilobase decrease in telomere length, 1.02; 95% CI, 0.83–1.26) (18). However, this study was limited by a small sample size of pancreatic cancer cases and lack of adjustment for potential confounding factors including smoking status (11, 15, 16). Given that the association of prediagnostic leukocyte telomere length and patient survival has not been universally observed across cancer types (18–23, 52–54), comprehensive analyses focusing on specific cancer types are warranted. The current study is the first prospective cohort study to provide evidence for an association between prediagnostic leukocyte telomere shortening and pancreatic cancer patient survival. Our results implicate telomere maintenance in the clinical course of pancreatic cancer after diagnosis, with potential therapeutic implications for this highly aggressive malignancy (55).

Telomere shortening and resultant chromosomal instability can occur in precursor lesions of pancreatic cancer, including pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN), and develop at increasing rates during progression

from precursor lesions to invasive ductal carcinoma (8–10). The surrogacy of leukocyte telomere length for cellular aging, telomere length in pancreatic tissue, and exposure to cancer risk factors may underline the association of shorter prediagnostic leukocyte telomere length and reduced survival among patients with pancreatic cancer (15, 16). The dynamics of leukocyte telomere attrition may vary during the process of carcinogenesis (56), and notably, we found a stronger prognostic association of prediagnostic leukocyte telomere length measured at earlier time-points before pancreatic cancer diagnosis. These findings also implicate a potential latency period from initiation of impaired telomere maintenance to clinically significant alterations of pancreatic cancer characteristics. Further studies are needed to understand how leukocyte telomere shortening might modify the biology and thus clinical behavior of pancreatic cancer in human populations.

Our study has notable strengths, including a prospective study design and nearly complete follow-up (25, 26). The banked blood samples and extended follow-up time allowed for examination of prediagnostic leukocyte telomere shortening and pancreatic cancer survival while minimizing bias due to reverse causation. Importantly, our study population consisted of patients with all stages of pancreatic cancer who were diagnosed at hospitals throughout the U.S., which increases the generalizability of our findings and minimizes selection bias. Within our cohorts, the median survival times for patients with pancreatic cancer were similar to those in the National Cancer Database (57), supporting the validity of our cohorts as a representative sample of pancreatic cancer patients in the United States. Prospectively collected data allowed us to rigorously adjust for potential confounders and to evaluate effect modification by other prognostic factors.

Our study has several limitations. We analyzed the length of leukocyte telomeres rather than that of telomeres in pancreatic tissue; nonetheless, telomere length in leukocytes is reasonably correlated with that in cells from different tissues (58–60) and is a readily available biomarker that can be measured from peripheral blood. Our cohort studies collected limited data on cancer treatments, and chemotherapy regimens for our patients were not known (25, 26). Nonetheless, prediagnostic leukocyte telomere length is unlikely to be associated with choice of treatment regimen, and chemotherapy options available during the study period were primarily limited to 5-fluorouracil / folinic acid or gemcitabine. In addition, our results remained largely unchanged after adjusting for year of cancer diagnosis and cancer stage, which are major determinants of treatment strategies. Similarly, though we cannot rule out the possibility of unmeasured confounding, our multivariable models included a variety of known and potential variables associated with pancreatic cancer survival, and this adjustment did not significantly alter our results. The sample size of the current study limits statistical power in subgroup analyses, including for stratified analyses by individual cohort studies and patient characteristics. Overall mortality was used as the primary study endpoint rather than pancreatic cancer-specific mortality, and leukocyte telomere length may be associated with overall mortality in the general population (61, 62). However, pancreatic cancer is a highly lethal malignancy, and the majority of patients die from this disease, such that overall mortality is considered a reasonable surrogate for clinical outcomes of pancreatic cancer. Finally, our study population predominantly consisted of white participants. Given evidence on a differential association of leukocyte telomere length

with mortality outcomes by ethnicity (61, 62), our findings should be validated in a more racially diverse population.

In conclusion, shorter prediagnostic leukocyte telomere length was associated with worse clinical outcome in patients with pancreatic cancer from four large U.S. cohort studies.

While our findings require validation, this study suggests an important role of telomere shortening in patient survival after clinical diagnosis of pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
CI	confidence interval
CV	coefficient of variation
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
NHS	Nurses' Health Study
OS	overall survival
PCR	polymerase chain reaction

PHS	Physicians' Health Study
SNP	single nucleotide polymorphism
WHI	Women's Health Initiative

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Number at risk

Leukocyte telomere length	Months								
	0	6	12	18	24	30	36	42	48
Q5 (longest)	84	49	32	16	11	10	9	8	8
Q1 (shortest)	84	41	25	12	5	3	2	2	2

Figure 1.

Overall survival curves of patients with pancreatic cancer by prediagnostic leukocyte telomere length (quintile 1 [shortest] vs. quintile 5 [longest]). Survival probabilities were adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, or Women's Health Initiative; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown), body mass index (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²), diabetes status (yes or no), and cancer stage (localized, locally advanced, metastatic, or unknown).

Q1, quintile 1; Q5, quintile 5.

Figure 2.

Forest plot and meta-analysis of HRs for overall mortality per standard deviation decrease in prediagnostic leukocyte telomere length among patients with pancreatic cancer in the HPFS, NHS, PHS, and WHI. Squares and horizontal lines indicate cohort-specific multivariable-adjusted HRs and 95% CIs, respectively. Area of the square reflects cohort-specific weight (inverse of the variance). Diamond indicates pooled multivariable-adjusted HR (center) and 95% CI (width). HRs were adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, or Women's Health Initiative; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown), body mass index (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²), diabetes status (yes or no), and cancer stage (localized, locally advanced, metastatic, or unknown).

CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study; PHS, Physicians' Health Study; WHI, Women's Health Initiative.

Table 1.

Baseline characteristics of patients with pancreatic cancer

Characteristic ^a	Pancreatic cancer cases (n = 423)
Age at blood collection, years	64.7 ± 8.8
Age at cancer diagnosis, years	71.9 ± 7.8
Female sex	283 (66.9)
Race/ethnicity	
White	369 (87.2)
Black	16 (3.8)
Other	10 (2.4)
Unknown	28 (6.6)
Year of diagnosis	
1984–2000	219 (51.8)
2001–2008	204 (48.2)
Median time from blood collection to cancer diagnosis, years	6.1
Smoking status	
Never	183 (43.2)
Past	179 (42.3)
Current	57 (13.5)
Unknown	4 (1.0)
Body mass index, kg/m ²	26.5 ± 5.1
Physical activity, MET-hours/week	17.9 ± 22.9
History of diabetes	28 (6.6)
Cancer stage at diagnosis	
Localized	53 (12.5)
Locally advanced	103 (24.4)
Metastatic	194 (45.8)
Unknown	73 (17.3)
Median survival time by stage, months	
Localized	16

Characteristic ^a	Pancreatic cancer cases (<i>n</i> = 423)
Locally advanced	10
Metastatic	4

^aData are presented as mean ± standard deviation or number of patients (%), unless otherwise noted.

Abbreviation: MET, metabolic equivalent of task.

Table 2.

Overall survival among patients with pancreatic cancer by quintiles of prediagnostic leukocyte telomere length

	Leukocyte telomere length					P_{trend}^c
	Q5 (longest)	Q4	Q3	Q2	Q1 (shortest)	
Person-months	1,266	777	886	721	858	
No. of cases/deaths	84/79	85/78	85/80	85/82	84/82	
Median survival, months	8	6	7	5	5	
Age-adjusted HR (95% CI)	1 (referent)	1.27 (0.93–1.74)	1.29 (0.94–1.76)	1.42 (1.04–1.94)	1.29 (0.94–1.76)	0.06
Multivariable HR ^a (95% CI)	1 (referent)	1.20 (0.87–1.66)	1.08 (0.79–1.49)	1.36 (0.98–1.88)	1.39 (1.01–1.93)	0.04
Multivariable HR ^b (95% CI)	1 (referent)	1.18 (0.85–1.63)	1.07 (0.78–1.48)	1.37 (0.99–1.91)	1.38 (0.99–1.91)	0.04

^aThe Cox proportional hazards regression model was adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, or Women's Health Initiative; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown), body mass index (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²), diabetes status (yes or no), and cancer stage (localized, locally advanced, metastatic, or unknown).

^bFurther adjusted for time from blood collection to cancer diagnosis (< 5, 5–10, or ≥ 10 years).

^c P_{trend} was calculated by entering quintile-specific median values of leukocyte telomere length (continuous) in the Cox regression model.

Abbreviations: CI, confidence interval; HR, hazard ratio; Q1–5, quintiles 1–5.

Table 3.

Overall survival among patients with pancreatic cancer by quartiles of prediagnostic leukocyte telomere length, stratified by time from blood collection to cancer diagnosis

Time from blood collection to cancer diagnosis ^a	No. of cases	Multivariable HR (95% CI) for quartiles of leukocyte telomere length ^b				<i>P</i> _{trend} ^c
		Q4 (longest)	Q3	Q2	Q1 (shortest)	
0 to < 6.1 years	212	1 (referent)	1.05 (0.69–1.59)	0.79 (0.52–1.21)	1.10 (0.71–1.69)	0.96
6.1 years	211	1 (referent)	1.11 (0.74–1.68)	1.42 (0.93–2.17)	1.60 (1.02–2.50)	0.03

^a Dichotomized by the median value.

^b The Cox proportional hazards regression model was adjusted for age at diagnosis (continuous), cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, or Women's Health Initiative; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown), body mass index (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²), diabetes status (yes or no), and cancer stage (localized, locally advanced, metastatic, or unknown).

^c *P*_{trend} was calculated by entering quartile-specific median values of leukocyte telomere length (continuous) in the Cox regression model.

Abbreviations: CI, confidence interval; HR, hazard ratio; Q1–4, quartiles 1–4.

Table 4.

Overall survival among patients with pancreatic cancer by quartiles of prediagnostic leukocyte telomere length, stratified by covariates

Stratification variable	No. of cases	Multivariable HR (95% CI) for quartiles of leukocyte telomere length ^a				<i>P</i> _{interaction} ^b
		Q4 (longest)	Q3	Q2	Q1 (shortest)	
Sex						0.87
Female	283	1 (referent)	1.15 (0.81–1.63)	1.29 (0.92–1.82)	1.30 (0.88–1.92)	
Male	140	1 (referent)	1.00 (0.56–1.77)	1.07 (0.59–1.94)	1.23 (0.73–2.06)	
Smoking status						0.64
Never	183	1 (referent)	1.00 (0.62–1.63)	0.93 (0.60–1.45)	0.98 (0.61–1.60)	
Past	179	1 (referent)	0.87 (0.56–1.36)	1.73 (1.09–2.77)	1.46 (0.92–2.31)	
Current	57	1 (referent)	3.07 (0.98–9.62)	0.81 (0.27–2.45)	1.01 (0.32–3.16)	
Body mass index						0.99
< 30 kg/m ²	341	1 (referent)	1.04 (0.75–1.43)	1.20 (0.86–1.67)	1.23 (0.89–1.71)	
30 kg/m ²	82	1 (referent)	0.90 (0.41–1.99)	1.16 (0.55–2.43)	1.32 (0.58–3.01)	
Cancer stage						0.26
Localized	53	1 (referent)	1.48 (0.43–5.14)	1.44 (0.55–3.74)	1.67 (0.67–4.14)	
Locally advanced	103	1 (referent)	0.88 (0.49–1.60)	1.04 (0.54–2.03)	1.41 (0.70–2.81)	
Metastatic	194	1 (referent)	0.99 (0.65–1.52)	0.94 (0.61–1.47)	1.07 (0.67–1.71)	

^aThe Cox proportional hazards regression model was adjusted for the following covariates except for the stratification variable: age at diagnosis (continuous), cohort (Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, or Women's Health Initiative; also adjusted for sex), race/ethnicity (white, black, other, or unknown), year of diagnosis (continuous), smoking status (never, past, current, or unknown), body mass index (< 25, 25–29.9, 30–34.9, or ≥ 35 kg/m²), diabetes status (yes or no), and cancer stage (localized, locally advanced, metastatic, or unknown).

^b*P*_{interaction} was calculated by entering a cross-product term of quartile-specific median values of leukocyte telomere length (continuous) and stratification variable in the Cox regression model and evaluating likelihood ratio tests.

Abbreviations: CI, confidence interval; HR, hazard ratio; Q1–4, quartiles 1–4.