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A prospective study of leukocyte telomere length and risk of renal cell carcinoma

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Abstract

Background—It has been hypothesized that genomic instability related to telomere dysfunction may contribute to carcinogenesis. There is some evidence from case-control studies suggesting that short leukocyte telomere length (TL) may be associated with an increased risk of renal cell carcinoma (RCC); however, this association has not been investigated prospectively.

Methods—We conducted a nested case-control study (209 cases, 410 controls) of RCC risk in relation to pre-diagnostic leukocyte TL in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression.

Results—Leukocyte TL was not significantly associated with future risk of RCC (highest quartile vs. lowest: OR=0.8, 95% CI=0.5–1.5; $P_{\text{trend}}=0.6$). Analyses stratified by sex, age, and time from blood collection to RCC diagnosis were similarly null.

Conclusions—The results of this study, to our knowledge the first prospective investigation of its kind, do not support an association between pre-diagnostic leukocyte TL and risk of RCC.

Impact—In contrast to some earlier reports, our findings add to the evidence that leukocyte TL is not a biomarker of risk related to the etiology of RCC.

Keywords

telomeres; telomere length; renal cell carcinoma; kidney cancer

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Introduction

Telomeres, nucleotide repeats at chromosome ends, are essential for chromosomal stability. Telomeres become gradually shorter with each cell division due to inefficient replication at the ends of linear DNA. Although critically short telomeres trigger cellular senescence and death in normal cells, cancer cells continue to divide despite the resultant genomic instability. Telomere length (TL) in peripheral blood leukocytes is a suspected marker of cancer risk (1). Results of retrospective case-control studies of leukocyte TL and renal cell carcinoma (RCC) have been inconsistent; two small hospital-based studies reported inverse associations between TL and RCC (2, 3), whereas no association was observed in a large population-based study (4). To our knowledge, this association has not been investigated prospectively. To address this research gap, we evaluated RCC risk in relation to pre-diagnostic leukocyte TL in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Materials and Methods

Enrollment and specimen collection procedures in PLCO have been described (5). Briefly, 155,000 subjects between 55 and 74 years of age were enrolled through study centers in 10 U.S. cities between 1993 and 2001. Half of the subjects were randomized to the screening arm of the trial and provided non-fasting blood samples at six annual screening examinations for trial disease outcomes. In addition to the annual examinations, questionnaires were mailed to subjects annually to ascertain new cancer diagnoses, which were pathologically confirmed through medical record abstraction. The trial was approved by institutional review boards at the National Cancer Institute and the 10 study centers, and all subjects provided written informed consent.

We measured leukocyte TL in 209 histologically confirmed cases of RCC (ICD-O-2 C64.9) and 410 controls individually matched to each case by sex, baseline age (5-year categories), race (white, black, other), date of phlebotomy (4-month categories), and study year of blood collection. DNA was extracted from buffy coat using QIAamp DNA Blood Maxi Kits (Qiagen Inc., Valencia, CA). Methods for TL assays have been described (6). Briefly, telomere repeat (T) and single gene (S) copy numbers were measured in each sample and adjusted in comparison to standard reference DNA; the standardized T/S ratio characterizes relative TL. Samples were assayed in triplicate and the average T/S ratio was calculated. Samples for each case and the corresponding matched controls were analyzed consecutively on the same plate. The within-plate coefficient of variation (from 36 blinded quality control samples distributed evenly across nine plates) was 5.9%. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. Our study had 85% power to detect an OR of 0.5 (or 2.0) comparing the highest and lowest quartiles of TL. All analyses were conditioned on matched sets, and analyses further adjusted for body mass index (BMI), history of hypertension, and smoking status (never, former, current) were performed. We also conducted analyses stratified by sex, age at blood collection (55–64 years, 65–74 years), and time from blood collection to RCC diagnosis (<6 years, 6 years).

Results

Cases and controls had similar distributions of age, sex, and race (Table 1). Cases were more likely than controls to be obese and to have a history of hypertension. The proportion of never-smokers was slightly higher among controls. Among controls, we observed shorter TL among subjects who were older, male, non-Hispanic white, obese, and current smokers (Supplementary Table 1).

Pre-diagnostic leukocyte TL was not significantly associated with RCC (Table 2). Risk estimates did not differ by sex, age at blood collection, or time from blood collection to RCC diagnosis (Table 2). We did not observe differences by tumor grade or after restricting to clear cell RCC cases ($N_{\text{cases}}=192$; data not shown).

Discussion

This study is, to our knowledge, the first prospective investigation of leukocyte TL and RCC. Whereas short leukocyte TL was associated with increased RCC risk in two small hospital-based case-control studies [32 and 65 cases, respectively; refs. (2, 3)], no association was observed in a larger population-based case-control study [891 cases; ref. (4)]. Risk estimates for various malignancies have been inconsistent between prospective and retrospective studies (1); although short TL appears to be associated with cancer in studies conducted retrospectively, those conducted prospectively have generally found either no association or, for non-Hodgkin lymphoma and lung cancer, increased risk with longer TL (7, 8).

In summary, our prospective study was sufficiently powered to detect an association smaller in magnitude than what has been reported in previous retrospective studies [e.g., $OR=5.4$ comparing the lowest and highest quartiles in ref. (3)]. However, we found no evidence of association between pre-diagnostic leukocyte TL and RCC risk, suggesting that leukocyte TL is not a biomarker of risk related to the etiology of RCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1Distribution of selected characteristics of cases and controls^a

Characteristics	Cases (N=209)	Controls (N=410)
Age at baseline, years		
55–59	62 (29.7)	123 (30.0)
60–64	74 (35.4)	145 (35.4)
65–69	50 (23.9)	96 (23.4)
70–74	23 (11.0)	46 (11.2)
Sex		
Female	62 (29.7)	122 (29.8)
Male	147 (70.3)	288 (70.2)
Race		
White, non-Hispanic	187 (89.5)	367 (89.5)
Black, non-Hispanic	10 (4.8)	19 (4.6)
Other	12 (5.7)	24 (5.9)
Body mass index, kg/m ²		
25	45 (21.5)	125 (30.8)
>25–30	86 (41.2)	185 (45.6)
>30	78 (37.3)	96 (23.7)
Missing	0	4
Smoking status		
Never	85 (40.7)	185 (45.1)
Former	106 (50.7)	183 (44.6)
Current	18 (8.6)	42 (10.2)
History of hypertension		
No	117 (56.3)	271 (66.8)
Yes	91 (43.8)	135 (33.3)
Missing	1	4
Telomere length, median (IQR)	1.18 (0.98–1.43) ^b	1.16 (0.97–1.51)

Abbreviations: IQR, interquartile range

^aReported as frequency (%) unless otherwise noted. Missing values are excluded from percentages.^bP=0.9, Wilcoxon rank-sum test.

Table 2

Odds ratios for risk of renal cell carcinoma in relation to leukocyte telomere length, overall and stratified by sex, age, and time from blood collection to case diagnosis^a

Analysis	1 st Quartile	2 nd Quartile	3 rd Quartile	4 th Quartile	<i>P</i> _{trend} ^b
Overall					
Cases/Controls	51/103	49/102	64/103	45/102	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	0.9 (0.6–1.5)	1.2 (0.8–1.9)	0.9 (0.5–1.5)	0.6
Adjusted OR (95% CI) ^d	1.0 (Ref)	0.9 (0.6–1.5)	1.1 (0.7–1.7)	0.8 (0.5–1.5)	0.6
By sex^e					
<i>Men</i>					
Cases/Controls	39/84	33/68	49/67	26/69	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	1.0 (0.6–1.8)	1.5 (0.9–2.6)	0.8 (0.4–1.5)	0.4
Adjusted OR (95% CI) ^d	1.0 (Ref)	1.0 (0.6–1.8)	1.3 (0.8–2.4)	0.8 (0.4–1.7)	0.6
<i>Women</i>					
Cases/Controls	12/19	16/34	15/36	19/33	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	0.7 (0.3–1.9)	0.7 (0.3–1.7)	0.9 (0.3–2.5)	0.9
Adjusted OR (95% CI) ^d	1.0 (Ref)	0.8 (0.3–2.2)	0.5 (0.2–1.4)	0.8 (0.2–2.4)	0.7
By age at baseline^e					
<i>55–64 years</i>					
Cases/Controls	33/63	32/73	42/63	29/69	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	0.8 (0.5–1.5)	1.2 (0.7–2.2)	0.8 (0.4–1.5)	0.6
Adjusted OR (95% CI) ^d	1.0 (Ref)	0.8 (0.4–1.5)	1.0 (0.6–1.9)	0.8 (0.4–1.6)	0.6
<i>65–74 years</i>					
Cases/Controls	18/40	17/29	22/40	16/33	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	1.3 (0.5–3.0)	1.2 (0.5–2.7)	1.0 (0.4–2.6)	0.9
Adjusted OR (95% CI) ^d	1.0 (Ref)	1.3 (0.5–3.1)	1.1 (0.5–2.6)	1.0 (0.4–2.6)	0.8
By time from blood collection to case diagnosis					
<i><6y to RCC diagnosis</i>					
Cases/Controls	24/50	21/44	28/50	20/39	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	1.0 (0.5–2.0)	1.2 (0.6–2.4)	1.1 (0.5–2.4)	0.8
Adjusted OR (95% CI) ^d	1.0 (Ref)	0.9 (0.4–1.9)	1.0 (0.5–2.1)	1.0 (0.4–2.4)	>0.9
<i>6y to RCC diagnosis</i>					
Cases/Controls	27/53	28/58	36/53	25/63	
Unadjusted OR (95% CI) ^c	1.0 (Ref)	0.9 (0.5–1.7)	1.2 (0.6–2.3)	0.7 (0.3–1.5)	0.3
Adjusted OR (95% CI) ^d	1.0 (Ref)	0.9 (0.4–1.7)	1.0 (0.5–2.0)	0.7 (0.3–1.6)	0.5

^aAnalyses were performed using conditional logistic regression models. Quartiles of telomere length were assigned based on the distribution among controls as follows: 1st quartile, 0.97; 2nd quartile, 0.98–1.15; 3rd quartile, 1.16–1.50; 4th quartile, 1.51.

^bTests for trend were performed by assigning the within-category median for each quartile and analyzing these data as a continuous variable.

^cConditioned on matched sets.

^dConditioned on matched sets and adjusted for history of hypertension, smoking status, and body mass index.

^e $P_{\text{interaction}}$ 0.4, likelihood ratio test.