Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

A Prospective Study of Leukocyte Telomere Length and Risk of Renal Cell Carcinoma

Jonathan N. Hofmann[1], Qing Lan[1], Richard Cawthon[2], H. Dean Hosgood III[3], Brian Shuch[4], Lee E. Moore[1], Nathaniel Rothman[1], Wong-Ho Chow[5], and Mark P. Purdue[1]

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 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 prediagnostic leukocyte telomere length in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. ORs and 95% confidence intervals (CI) were estimated using conditional logistic regression.

Results: Leukocyte telomere length was not significantly associated with future risk of RCC (highest quartile vs. lowest: OR, 0.8; 95% CI, 0.5–1.5; $P_{trend} = 0.6$). 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 prediagnostic leukocyte telomere length and risk of RCC.

Impact: In contrast to some earlier reports, our findings add to the evidence that leukocyte telomere length is not a biomarker of risk related to the etiology of RCC. *Cancer Epidemiol Biomarkers Prev; 22(5); 997–1000. ©2013 AACR.*

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 in peripheral blood leukocytes is a suspected marker of cancer risk (1). Results of retrospective case–control studies of leukocyte telomere length and renal cell carcinoma (RCC) have been inconsistent; 2 small hospital-based studies reported inverse associations between telomere length 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 prediagnostic leukocyte telomere length in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Materials and Methods

Enrollment and specimen collection procedures in PLCO have been described in ref. (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 nonfasting blood samples at 6 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.

Authors' Affiliations: [1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [2]Department of Human Genetics, University of Utah, Salt Lake City, Utah; [3]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York; [4]Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; and [5]Department of Epidemiology, MD Anderson Cancer Center, Houston, Texas

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Jonathan N. Hofmann, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS 8113, Bethesda, MD 20892. Phone: 301-402-2605; Fax: 301-402-1819; E-mail: hofmannjn@mail.nih.gov

doi: 10.1158/1055-9965.EPI-13-0142

We measured leukocyte telomere length 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.). Methods for telomere length assays have been described (6). Briefly, telomere repeat (T) and single gene (S) copy numbers were measured in each sample and adjusted in comparison with standard reference DNA; the standardized T:S ratio characterizes relative telomere length. 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 9 plates) was 5.9%. ORs and 95% confidence intervals (CI) were estimated using conditional logistic regression. Our study had 85% power to detect an OR of $\leq$0.5 (or $\geq$2.0) comparing the highest and lowest quartiles of telomere length. All analyses were conditioned on matched sets, and analyses further adjusted for body mass index (BMI), history of hypertension, and smoking status (never, former, and current) were conducted. 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, $\geq$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 telomere length among subjects who were older, male, non-Hispanic white, obese, and current smokers (Supplementary Table S1).

Prediagnostic leukocyte telomere length 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_{cases} = 192; data not shown).

Table 1. Distribution of selected characteristics of cases and controls[a]

Characteristics	Cases (N = 209)	Controls (N = 410)
Age at baseline, y		
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)
BMI, kg/m^2		
$\leq$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)

Abbreviation: IQR, interquartile range.

[a]Reported as frequency (%) unless otherwise noted. Missing values are excluded from percentages.

[b]P = 0.9, Wilcoxon rank-sum test.

Discussion

This study is, to our knowledge, the first prospective investigation of leukocyte telomere length and RCC. Although short leukocyte telomere length was associated with increased RCC risk in 2 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 telomere length seems 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 telomere length (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 prediagnostic leukocyte telomere length and RCC risk, suggesting that leukocyte telomere length is not a biomarker of risk related to the etiology of RCC.

Table 2. ORs for risk of RCC in relation to leukocyte telomere length, overall and stratified by sex, age, and time from blood collection to case diagnosis[a]

Analysis	First quartile	Second quartile	Third quartile	Fourth quartile	P_{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]					
Men					
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
Women					
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]					
55–64 y					
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
65–74 y					
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					
<6y to RCC diagnosis					
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
≥6y to RCC diagnosis					
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

[a]Analyses were conducted using conditional logistic regression models. Quartiles of telomere length were assigned on the basis of the distribution among controls as follows: first quartile, ≤0.97; second quartile, 0.98–1.15; third quartile, 1.16–1.50; fourth quartile, ≥1.51.
[b]Tests for trend were conducted by assigning the within-category median for each quartile and analyzing these data as a continuous variable.
[c]Conditioned on matched sets.
[d]Conditioned on matched sets and adjusted for history of hypertension, smoking status, and BMI.
[e]$P_{interaction} \geq 0.4$, likelihood ratio test.

Disclosure of Potential Conflicts of Interest

R. Cawthon has ownership interest (including patents) on method of measuring telomere length and is a consultant/advisory board member of Scientific Advisory Board, Telome Health, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.N. Hofmann, Q. Lan, L.E. Moore, N. Rothman, M.P. Purdue
Development of methodology: J.N. Hofmann, R. Cawthon, M.P. Purdue
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.N. Hofmann, R. Cawthon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.N. Hofmann, Q. Lan, H.D. Hosgood, B. Shuch, L.E. Moore, W.-H. Chow, M.P. Purdue
Writing, review, and/or revision of the manuscript: J.N. Hofmann, Q. Lan, R. Cawthon, H.D. Hosgood, B. Shuch, L.E. Moore, N. Rothman, W.-H. Chow, M.P. Purdue
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.N. Hofmann
Study supervision: M.P. Purdue

Acknowledgments

The authors thank the Screening Center investigators and staff of the PLCO Cancer Screening Trial; Mr. Tom Riley, Matthew Chaloux, and other staff, Information Management Services, Inc.; Ms. Barbara O'Brien and staff, Westat, Inc.; and Ms. Amy Hutchinson and Sally Larson, Frederick National Laboratory. The authors also thank the study participants for their contributions to make this study possible.

Grant Support

This research was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, Department of Health and Human Services (DHHS).

Received February 4, 2013; accepted February 10, 2013; published OnlineFirst March 19, 2013.

References

1. Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA. The association of telomere length and cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2011;20:1238–50.
2. Wu X, Amos CI, Zhu Y, Zhao H, Grossman BH, Shay JW, et al. Telomere dysfunction: a potential cancer predisposition factor. J Natl Cancer Inst 2003;95:1211–8.
3. Shao L, Wood CG, Zhang D, Tannir NM, Matin S, Dinney CP, et al. Telomere dysfunction in peripheral lymphocytes as a potential predisposition factor for renal cancer. J Urol 2007;178(4 Pt 1):1492–6.
4. Hofmann JN, Baccarelli A, Schwartz K, Davis FG, Ruterbusch JJ, Hoxha M, et al. Risk of renal cell carcinoma in relation to blood telomere length in a population-based case–control study. Br J Cancer 2011;105:1772–5.
5. Hayes RB, Reding D, Kopp W, Subar AF, Bhat N, Rothman N, et al. Etiologic and early marker studies in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Control Clin Trials 2000;21(6 Suppl):349S–55S.
6. Cawthon RM. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. Nucleic Acids Res 2009;37:e21.
7. Lan Q, Cawthon R, Shen M, Weinstein SJ, Virtamo J, Lim U, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of non-Hodgkin lymphoma. Clin Cancer Res 2009;15:7429–33.
8. Shen M, Cawthon R, Rothman N, Weinstein SJ, Virtamo J, Hosgood HD, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. Lung Cancer 2011;73:133–7.

A Prospective Study of Leukocyte Telomere Length and Risk of Renal Cell Carcinoma

Jonathan N. Hofmann, Qing Lan, Richard Cawthon, et al.

Cancer Epidemiol Biomarkers Prev 2013;22:997-1000. Published OnlineFirst March 19, 2013.