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Accessibility
Short Communication

Risk of renal cell carcinoma in relation to blood telomere length in a population-based case–control study

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BACKGROUND: There are few known risk factors for renal cell carcinoma (RCC). Two small hospital-based case–control studies suggested an association between short blood telomere length (TL) and increased RCC risk.

METHODS: We conducted a large population-based case–control study in two metropolitan regions of the United States comparing relative TL in DNA derived from peripheral blood samples from 891 RCC cases and 894 controls. Odds ratios and 95% confidence intervals were estimated using unconditional logistic regression in both unadjusted and adjusted models.

RESULTS: Median TL was 0.85 for both cases and controls (P = 0.40), and no differences in RCC risk by quartiles of TL were observed.

CONCLUSION: These data do not support the hypothesis that blood TL is associated with RCC. This population-based case–control study is, to our knowledge, the largest investigation to date of TL and RCC.

Keywords: telomere; renal cell carcinoma; kidney cancer

Telomeres are nucleotide repeats and a protein complex at chromosome ends that are essential for chromosomal stability. Telomere attrition occurs with each cell division due to inefficient replication at the ends of linear DNA. Critically short telomeres trigger cellular senescence and death, but cancer cells divide despite the resultant genomic instability. Telomere length (TL) is a suspected marker of cancer risk (De Lange, 2005). Two small hospital-based case–control studies reported an increased risk of renal cell carcinoma (RCC) in relation to shorter TL (Wu et al, 2003; Shao et al, 2007). To follow up on these findings, we evaluated RCC risk in relation to TL in a large case–control study.

MATERIALS AND METHODS

Study population, data and sample collection, and sample processing

Subject recruitment and data and specimen collection methods have been described (Colt et al, 2011). Briefly, this population-based case–control study of Caucasians and African Americans was conducted in Detroit, MI, USA (Wayne, Oakland, and Macomb Counties) from 2002–2007, and in Chicago, IL, USA (Cook County) in 2003; according to US census estimates from 2000, the populations of these two metropolitan areas had generally similar racial distributions (56.3% Caucasian and 26.1% African American in Cook County; 68.9% Caucasian and 25.0% African American in Wayne, Oakland, and Macomb Counties, combined). To maximise enrolment of African Americans, we over-sampled African American cases relative to Caucasian cases, and we frequency matched controls to cases at a 2:1 ratio for African Americans and a 1:1 ratio for Caucasians to increase statistical power for analyses stratified by race. Subjects with stored blood samples (whole blood or buffy coat) were included in this analysis. Eight cases with benign tumours, non-RCC histology, or cancer in a transplanted kidney were excluded. Telomere length could not be measured for one control subject, who was also excluded, leaving 891 cases (658 Caucasians and 233 African Americans) and 894 controls (550 Caucasians and 344 African Americans). Blood samples were collected from cases and controls at the time of the personal interview. Among cases, the median time from RCC diagnosis to blood sample collection was about 4 months. Samples of DNA were extracted via Qiagen kits; DNA was derived from whole blood samples for most study subjects (cases: 627 whole blood, 264 buffy coat; controls: 768 whole blood, 126 buffy coat). The distribution of the source material for DNA extraction was similar for each study centre. Study procedures were approved by Institutional
Review Boards at collaborating institutions, and written informed consent was obtained from all subjects.

**TL measurements**

A quantitative PCR assay was used to measure TL; assay methods have been described (Cawthon, 2002). Briefly, telomere repeat (T) and single gene (S) copy numbers were measured in individual samples and adjusted in comparison to standard reference DNA; the standardised T/S ratio characterises relative TL. In TL measurements for blinded duplicate QC samples from 59 subjects, the coefficient of variation (CV) was 9.9% and the intraclass correlation coefficient was 0.85 (95% confidence interval (CI): 0.76, 0.91).

**Statistical analysis**

Telomere length data were natural log-transformed to achieve a normal distribution. We compared TL between cases and controls, and evaluated differences in TL by demographic and personal characteristics among controls in bivariate and multivariate analyses. Odds ratios (ORs) and 95% CIs were calculated using unconditional logistic regression. Quartiles of TL were determined based on the distribution among controls. Adjusted analyses included terms for age (10-year categories), sex, race, smoking, body mass index (BMI), history of hypertension, education, study centre, and material type (whole blood or buffy coat). Analyses stratified by these covariates, tumour stage/grade, RCC treatment modality, and time from RCC diagnosis to blood collection were also performed.

**RESULTS**

Cases and controls had similar age and sex distributions. Cases were more likely to be obese (BMI ≥ 30), to smoke, and to have a history of hypertension, as reported previously (Karami et al., 2010). The vast majority of cases with treatment information available had surgery alone without adjuvant therapy (N = 803; 92%), and most cases with information on stage at diagnosis had localised disease (N = 611; 81%).

Median relative TL (5th–95th percentile distributions) was 0.85 (0.58–1.25) and 0.85 (0.58–1.23) for cases and controls, respectively (P = 0.40, Wilcoxon rank sum test). A box plot showing the distribution of TL measurements among cases and controls is available online (Supplementary Figure I). No differences in TL between cases and controls were observed after stratifying by material type. The expected age-related decline in TL was observed in both cases and controls. In multivariate analyses among controls, TL was significantly longer among African Americans than among Caucasians (P < 0.001), and we observed a borderline significant association between hypertension and shorter TL (P = 0.07; Table 1).

No overall associations between TL and RCC were observed (Table 2). Analyses stratified by sex, race, age, or other variables did not reveal any consistent subgroup-specific associations between TL and RCC. No differences in the relationship between TL and RCC by tumour stage (localised vs other) were observed, nor when we restricted our analysis to cases treated by surgery alone. We did not observe any differences in TL by days from RCC diagnosis to blood collection (adjusted β = −2.95 × 10⁻⁵; 95% CI: −9.01 × 10⁻⁵; 3.11 × 10⁻⁵), and risk estimates did not differ after stratifying by time since diagnosis (data not shown).

**DISCUSSION**

The results of this case–control study do not support the hypothesis that blood TL is associated with RCC. Our study did not replicate findings from two hospital-based case–control studies with 32 and 65 RCC cases, respectively, that reported an inverse association between TL and RCC (Wu et al., 2003; Shao et al., 2007). Both prior studies measured TL using a Q-FISH assay; it has been demonstrated that Q-FISH measurements are highly correlated with measurements by the QPCR method used in this study (Cawthon, 2002). Because measurements in our study were highly reproducible in blind replicates (CV = 9.9%), it is unlikely that measurement error could explain the differences in findings between our study and previous studies.

This population-based case–control study is, to our knowledge, the largest investigation of TL and RCC to date. We had 89% power to detect a trend in ORs with decreasing quartiles of TL assuming an inverse association between TL and RCC (Wu et al., 2003; Shao et al., 2003; Demissie et al., 2006; Mirabello et al., 2009), which supports the validity of these findings. Differences in TL by race are inconsistent in previous studies (Hunt et al., 2008; Roux et al., 2009) and additional research is needed to confirm these findings. Numerous studies have investigated TL in relation to smoking and BMI (Wu et al., 2003; Demissie et al., 2006; Mirabello et al., 2009).

**Table 1** Determinants of blood telomere length among controls

| Variable                  | N    | Geometric mean (95% CI) | Difference in geometric mean (95% CI) |
|---------------------------|------|------------------------|--------------------------------------|
| Age category              |      |                        |                                      |
| <45                       | 128  | 1.00 (0.97, 1.04)       | Ref                                  |
| 45–54                     | 198  | 0.88 (0.85, 0.91)       | −10% (−15%, −6%)*                    |
| 55–64                     | 255  | 0.82 (0.80, 0.85)       | −15% (−19%, −11%)*                   |
| 65–74                     | 237  | 0.79 (0.77, 0.82)       | −18% (−22%, −14%)*                   |
| 75+                       | 76   | 0.78 (0.74, 0.83)       | −18% (−23%, −13%)*                   |
| P<0.001                   |      |                        |                                      |
| Sex                       |      |                        |                                      |
| Female                    | 381  | 0.86 (0.84, 0.89)       | Ref                                  |
| Male                      | 513  | 0.83 (0.82, 0.85)       | −2% (−5%, 1%)                        |
| Race                      |      |                        |                                      |
| Caucasian                 | 550  | 0.82 (0.81, 0.84)       | Ref                                  |
| African American          | 344  | 0.89 (0.86, 0.91)       | 9% (5%, 12%)*                        |
| Hypertension              |      |                        |                                      |
| Never                     | 525  | 0.87 (0.85, 0.89)       | Ref                                  |
| Ever                      | 364  | 0.81 (0.79, 0.83)       | −3% (−6%, 0%)**                      |
| Smoking status            |      |                        |                                      |
| Never                     | 346  | 0.86 (0.84, 0.89)       | Ref                                  |
| Occasional                | 41   | 0.87 (0.80, 0.95)       | −1% (−7%, 6%)                        |
| Former                    | 331  | 0.83 (0.81, 0.85)       | 0% (−3%, 3%)                         |
| Current                   | 175  | 0.85 (0.82, 0.88)       | −2% (−6%, 2%)                        |
| BMI                        |      |                        |                                      |
| <25                       | 256  | 0.85 (0.83, 0.88)       | Ref                                  |
| 25–29.9                   | 366  | 0.84 (0.82, 0.86)       | 2% (−2%, 5%)                         |
| 30–34.9                   | 155  | 0.86 (0.82, 0.89)       | 3% (−2%, 7%)                         |
| 35+                       | 114  | 0.84 (0.80, 0.88)       | 0% (−5%, 5%)                         |
| Source of DNA specimen     |      |                        |                                      |
| Whole blood               | 768  | 0.83 (0.82, 0.85)       | Ref                                  |
| Buffy coat                | 126  | 0.95 (0.91, 0.99)       | 10% (5%, 15%)*                       |

Abbreviations: CI = confidence interval; BMI = body mass index. *Telomere length measurements were expressed as the standardised T/S ratio, and data were natural log-transformed for all analyses. Each variable was evaluated after adjusting for all other covariates reported above as well as study centre and level of education. Nine controls with missing data for any variable were excluded from this analysis. The percent difference in the geometric mean relative to the reference category was estimated using the formula (exp(b1) − 1). **P<0.001. ***P = 0.07.
| Telomere length quartile<sup>b</sup> | \( N_{\text{cases}} \) | \( N_{\text{controls}} \) | Unadjusted OR (95% CI) | Adjusted OR (95% CI)<sup>c</sup> |
|-------------------------------|----------------|----------------|----------------------|----------------------|
| Overall                       |                |                |                      |                      |
| 4th Quartile                  | 259            | 222            | Ref                  | Ref                  |
| 3rd Quartile                  | 177            | 224            | 0.68 (0.52, 0.88)    | 0.69 (0.51, 0.93)    |
| 2nd Quartile                  | 242            | 224            | 0.93 (0.72, 1.20)    | 0.90 (0.67, 1.20)    |
| 1st Quartile                  | 213            | 224            | 0.82 (0.63, 1.06)    | 0.79 (0.59, 1.07)    |
| \( P_{\text{trend}} = 0.29 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.25 \) |                |                |                      |                      |
| Stratified analyses           |                |                |                      |                      |
| Sex                           |                |                |                      |                      |
| Women                         |                |                |                      |                      |
| 4th Quartile                  | 116            | 102            | Ref                  | Ref                  |
| 3rd Quartile                  | 80             | 108            | 0.65 (0.44, 0.96)    | 0.68 (0.43, 1.09)    |
| 2nd Quartile                  | 104            | 82             | 1.12 (0.75, 1.65)    | 1.11 (0.69, 1.79)    |
| 1st Quartile                  | 69             | 89             | 0.68 (0.45, 1.03)    | 0.60 (0.36, 0.99)    |
| \( P_{\text{trend}} = 0.28 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.17 \) |                |                |                      |                      |
| Men                           |                |                |                      |                      |
| 4th Quartile                  | 143            | 120            | Ref                  | Ref                  |
| 3rd Quartile                  | 138            | 142            | 0.82 (0.58, 1.14)    | 0.82 (0.56, 1.19)    |
| 2nd Quartile                  | 144            | 135            | 0.90 (0.64, 1.25)    | 0.90 (0.61, 1.32)    |
| \( P_{\text{trend}} = 0.59 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.66 \) |                |                |                      |                      |
| Race                          |                |                |                      |                      |
| African American              |                |                |                      |                      |
| 4th Quartile                  | 80             | 107            | Ref                  | Ref                  |
| 3rd Quartile                  | 44             | 86             | 0.87 (0.63, 1.19)    | 0.97 (0.68, 1.39)    |
| 2nd Quartile                  | 57             | 87             | 0.88 (0.56, 1.36)    | 0.73 (0.43, 1.23)    |
| 1st Quartile                  | 52             | 64             | 1.09 (0.68, 1.73)    | 0.84 (0.48, 1.46)    |
| \( P_{\text{trend}} = 0.04 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.32 \) |                |                |                      |                      |
| Caucasian                     |                |                |                      |                      |
| 4th Quartile                  | 179            | 115            | Ref                  | Ref                  |
| 3rd Quartile                  | 133            | 138            | 0.62 (0.44, 0.86)    | 0.69 (0.48, 0.99)    |
| 2nd Quartile                  | 185            | 137            | 0.87 (0.63, 1.20)    | 0.97 (0.68, 1.39)    |
| 1st Quartile                  | 161            | 160            | 0.65 (0.47, 0.89)    | 0.76 (0.53, 1.10)    |
| \( P_{\text{trend}} = 0.85 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.42 \) |                |                |                      |                      |
| Age                           |                |                |                      |                      |
| Under 60 years of age         |                |                |                      |                      |
| 4th Quartile                  | 177            | 160            | Ref                  | Ref                  |
| 3rd Quartile                  | 99             | 123            | 0.73 (0.52, 1.02)    | 0.81 (0.55, 1.20)    |
| 2nd Quartile                  | 103            | 105            | 0.89 (0.63, 1.25)    | 1.00 (0.67, 1.49)    |
| 1st Quartile                  | 80             | 67             | 1.08 (0.73, 1.59)    | 1.29 (0.83, 2.02)    |
| \( P_{\text{trend}} = 0.99 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.36 \) |                |                |                      |                      |
| 60+ years of age              |                |                |                      |                      |
| 4th Quartile                  | 82             | 62             | Ref                  | Ref                  |
| 3rd Quartile                  | 78             | 101            | 0.58 (0.38, 0.91)    | 0.60 (0.38, 0.96)    |
| 2nd Quartile                  | 139            | 119            | 0.88 (0.59, 1.33)    | 0.85 (0.55, 1.32)    |
| 1st Quartile                  | 133            | 157            | 0.64 (0.43, 0.96)    | 0.62 (0.40, 0.95)    |
| \( P_{\text{trend}} = 0.13 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.09 \) |                |                |                      |                      |
| Source of DNA specimen         |                |                |                      |                      |
| Whole blood<sup>d</sup>       |                |                |                      |                      |
| 4th Quartile                  | 145            | 192            | Ref                  | Ref                  |
| 3rd Quartile                  | 139            | 192            | 0.96 (0.71, 1.30)    | 0.78 (0.55, 1.10)    |
| 2nd Quartile                  | 180            | 192            | 1.24 (0.92, 1.67)    | 0.88 (0.63, 1.23)    |
| 1st Quartile                  | 163            | 192            | 1.12 (0.83, 1.52)    | 0.79 (0.56, 1.11)    |
| \( P_{\text{trend}} = 0.23 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.25 \) |                |                |                      |                      |
| Buffy coat<sup>e</sup>        |                |                |                      |                      |
| 4th Quartile                  | 72             | 32             | Ref                  | Ref                  |
| 3rd Quartile                  | 55             | 31             | 0.79 (0.43, 1.45)    | 0.68 (0.35, 1.32)    |
| 2nd Quartile                  | 68             | 32             | 0.94 (0.52, 1.71)    | 0.80 (0.41, 1.57)    |
| 1st Quartile                  | 69             | 31             | 0.99 (0.55, 1.79)    | 1.11 (0.56, 2.21)    |
| \( P_{\text{trend}} = 0.90 \) |                |                |                      |                      |
| \( P_{\text{trend}} = 0.70 \) |                |                |                      |                      |

**Abbreviations:** OR = odds ratio; CI = confidence interval; BMI = body mass index. Telomere length measurements were expressed as the standardised T/S ratio. Quartiles were determined based on the distribution of telomere length measurements among controls. Cut points were defined as follows: Q1, ≤0.7288; Q2, 0.7289 – 0.8535; Q3, 0.8536 – 0.9795; and Q4, ≥0.9796. Adjusted for the following covariates: sex, age, race, smoking status, BMI, history of hypertension, level of education, study centre (Detroit or Chicago), and material type (whole blood or buffy coat). In all, 30 subjects with missing data for smoking status, BMI, or history of hypertension were excluded from this analysis. Quartiles based on the distribution of telomere length measurements among controls with whole blood samples. Cut points were defined as follows: Q1, ≤0.7197; Q2, 0.7198 – 0.8341; Q3, 0.8342 – 0.9633; and Q4, ≥0.9634. Quartiles based on the distribution of telomere length measurements among controls with buffy coat samples. Cut points were defined as follows: Q1, ≤0.8323; Q2, 0.8324 – 0.9651; Q3, 0.9652 – 1.1048; and Q4, ≥1.1049.
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REFERENCES

Cawthon RM (2002) Telomere measurement by quantitative PCR. Nucleic Acids Res 30: e47

Colt JS, Schwartz K, Graubard BI, Davis F, Ruterbusch J, Digiato R, Purdie M, Rothman N, Wacholder S, Chow WH (2011) Hypertension and risk of renal cell carcinoma among white and black Americans. Epidemiology 22(6): 797 – 804

De Lange T (2005) Telomere-related genome instability in cancer. Cold Spring Harb Symp Quant Biol 70: 197 – 204

Demisseis S, Levy D, Benjamin J, Cupples LA, Gardner JP, Herbert A, Kimura M, Larson MG, Meigs JB, Keaney JF, Aviv A (2006) Insulin resistance, oxidative stress, hypertension, and leukocyte telomere length in men from the Framingham Heart Study. Aging Cell 5: 325 – 330

Fitzpatrick AL, Kronmal RA, Kimura M, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Hardikar S, Aviv A (2011) Leukocyte telomere length and mortality in the Cardiovascular Health Study. J Gerontol A Biol Sci Med Sci 66: 421 – 429

Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A (2008) Leukocyte telomeres are longer in African Americans than in whites: the National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. Aging Cell 7: 451 – 458

Karami S, Schwartz K, Purdie MP, Davis FG, Ruterbusch J, Munuo SS, Wacholder S, Graubard BI, Colt JS, Chow WH (2010) Family history of cancer and renal cell cancer risk in Caucasians and African Americans. Br J Cancer 102: 1676 – 1680

Kim S, Parks CG, DeRoo LA, Chen H, Taylor JA, Cawthon RM, Sandler DP (2009) Obesity and weight gain in adulthood and telomere length. Cancer Epidemiol Biomarkers Prev 18: 816 – 820

Lee M, Martin H, Firpo MA, Demerath EW (2011) Inverse association between adiposity and telomere length: the Fels Longitudinal Study. Am J Hum Biol 23: 100 – 106

Mirabello L, Huang WY, Wong JY, Chatterjee N, Reding D, Crawford ED, De Vivo I, Hayes RB, Savage SA (2009) The association between leukocyte telomere length and cigarette smoking, dietary and physical variables, and risk of prostate cancer. Aging Cell 8: 405 – 413

Nordjall K, Eliasson M, Stegmayr B, Melander O, Nilsson P, Roos G (2008) Telomere length is associated with obesity parameters but with a gender difference. Obesity (Silver Spring) 16: 2682 – 2689

Pooley KA, Sandhu MS, Tyrer J, Shah M, Driver KE, Luben RN, Bingham SA, Ponder BA, Pharoah PD, Khaw KT, Easton DF, Dunning AM (2010) Telomere length in prospective and retrospective cancer case-control studies. Cancer Res 70b: 3170 – 3176

Roux AV, Ranjit N, Jenny NS, Shea S, Cushman M, Fitzpatrick A, Seemann T (2009) Race/ethnicity and telomere length in the Multi-Ethnic Study of Atherosclerosis. Aging Cell 8: 251 – 257

Shao L, Wood CG, Zhang D, Tannir NM, Matsin S, Dinney CP, Wu X (2007) Telomere dysfunction in peripheral lymphocytes as a potential predisposition factor for renal cancer. J Urol 178: 1492 – 1496

Shen M, Cawthon R, Rothman N, Weinstein SJ, Virtamo J, Hosgood HD, Hu W, Lim U, Albane D, Lan Q (2011) A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. Lung Cancer 73: 133 – 137

Svenson U, Ljungberg B, Roos G (2009) Telomere length in peripheral blood predicts survival in clear cell renal cell carcinoma. Cancer Res 69: 2896 – 2901

Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviny A, Spector TD (2005) Obesity, cigarette smoking, and telomere length in the Multi-Ethnic Study of Atherosclerosis. Aging Cell 4: 2682 – 2689

Wentzensen IM, Mirabello L, Pfeiffer RM, Savage SA (2011) The association of telomere length and cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 20(6): 1238 – 1250

Wu X, Anos CI, Zhu Y, Zhao H, Grossman BH, Shav JW, Luo S, Hong WK, Spitz MR (2003) Telomere dysfunction: a potential cancer predisposition factor. J Natl Cancer Inst 95: 1211 – 1218