Am J Cancer Res 2020;10(10):3428-3439
www.ajcr.us /ISSN:2156-6976/ajcr0117285

Original Article

Prognostic value of leukocyte telomere length in renal cell carcinoma patients

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Received June 30, 2020; Accepted July 9, 2020; Epub October 1, 2020; Published October 15, 2020

Abstract: Telomeres play important roles in cancer initiation and progression. Leukocyte telomere length (LTL) can modulate cancer risk and outcome. We hypothesize that genetically predicted short LTL is associated with worse prognosis in renal cell carcinoma (RCC). A total of 1,086 histologically confirmed RCC patients were included in this study. A weighted genetic risk score (GRS) predictive of LTL was constructed using 10 confirmed LTL-associated single nucleotide polymorphisms (SNPs). The associations of individual SNPs and GRS with recurrence and survival were determined by multivariate Cox proportional hazards analysis. In individual SNP analysis, long LTL-associated allele of rs7675998 in NAF1 gene at chromosome 4 was significantly associated with a reduced risk of recurrence (HR=0.85, 95% CI, 0.73-0.99, P=0.043), while the long LTL-associated allele of rs10936599 in TERC at chromosome 3 conferred a reduced risk of death (HR=0.85, 95% CI, 0.73-1.00, P=0.047). More importantly, genetically predicted LTL was associated with both recurrence and survival. Dichotomized at the median value of GRS, patients with low GRS (indicating short LTL) exhibited significantly increased risks of recurrence (HR=1.26, 95% CI, 1.03-1.54, P=0.025) and death (HR=1.23, 95% CI, 1.00-1.50, P=0.045). Hence, we concluded that genetically predicted short LTL is associated with worse prognosis in RCC patients.

Keywords: Renal cell carcinoma, leukocyte telomere length, recurrence, survival, genetic risk score (GRS), Mendelian randomization

Introduction

Renal cell carcinoma (RCC) accounts for about 85% of adult kidney cancers and is the most lethal genitourinary cancer. The incidence of RCC has been steadily rising by 2-4% per year in the past four decades until recent years when the incidence rate stabilized [1, 2]. About two thirds of patients with RCC have localized diseases at diagnosis and the remaining one third of patients present with regional and distant metastatic RCC [1]. The clinical management of RCC has evolved significantly in the past decade when novel surgical and systemic therapies have improved the prognosis of RCC [3]. Although patients with localized RCC can be cured by nephrectomy, about 40% of patients will develop recurrence/metastasis after surgical resection and eventually die from this disease [3]. The success of targeted and immune checkpoint therapies in metastatic RCC has generated intense interest in using these novel therapies in adjuvant setting to prevent diseases recurrence/metastasis. To improve prognosis of surgically resected RCC, effective adjuvant therapy is clearly needed for high risk RCC. However, to date, the only FDA approved systemic adjuvant therapy for RCC is sunitinib, which offered a 2-month disease-free survival benefit accompanied by significant drug-related toxicities [4]. Many clinical trials of targeted and immune therapy for localized, high-risk RCC have been completed or are ongoing [5, 6]. Whereas efficacy has been mostly disappointing, toxicity has been consistently a major concern. Patient selection based on accurate risk stratification algorithm is obviously a pre-requisite for successful adjuvant

therapy. There are several clinically used nomograms for predicting recurrence risk in surgically resected RCC patients that rely solely on clinicopathologic variables (e.g., histology, tumor size, TNM stage, Fuhrman grade, and performance status) [5], but these clinical variable-based prognostic models are not sufficient. Identifying independent biomarkers that can supplement clinical variables to determine which patients are most likely to recur/metastasize after surgery has tremendous clinical value [7, 8].

Telomeres cap each chromosome and protect its integrity. Critically short telomeres lead to genomic instability and cancer development. Telomere length inversely correlates with age, and there is large inter-individual variation of telomere length among people of the same ages [9, 10]. Because telomere length is highly correlated between blood and different tissues in newborns and adults [11-13], telomere length in easily accessible tissues such as blood can serve as a surrogate for telomere length in other tissues. Leukocyte telomere length (LTL) is therefore often used in human population studies to investigate the relationship between a person's telomere length and disease risks [14-18]. A recent study showed that short LTL was associated with poorer RCC-specific survival in two independent patient cohorts [19]. However, there has not been any report of LTL with recurrence in RCC patients.

Recently, there has been increasing use of genetic variants as instrumental variables to estimate LTL and determine its association with disease risks, an approach called Mendelian randomization (MR) [20-23]. There are three assumptions in MR studies: 1) the selected genetic variants are associated with the studied risk factor/biomarker (e.g., LTL); 2) the genetic variants are independent of confounding factors; and 3) the genetic variants only influence disease risk through their effects on the risk factor/biomarker. Large genome-wide association studies (GWAS) have identified at least ten independent genomic regions associated with *L*TL [24-26]. Single nucleotide polymorphisms (SNPs) in these regions are believed to meet the assumptions of MR studies and have been used as genetic instruments to assess the causal relationship between LTL and diseases risks [20-22, 27-34]. No study has applied an MR approach to study LTL in RCC prognosis. In this study, for the first time, we evaluated the roles of genetically predicted LTL in the recurrence and survival of RCC patients.

Materials and methods

Study population and data collection

This study consisted of a total of 1,086 patients of European ancestry with histologically confirmed RCC from the University of Texas MD Anderson Cancer Center. The patients were newly diagnosed patients who were treated at MD Anderson. Questionnaire data were obtained via personal interview by trained MD Anderson study interviewers. The questionnaire collects data on demographics, tobacco exposure, occupational history, family history of cancer, medical history, and medication. Clinical and follow-up data were abstracted from medical records. Information include comorbid conditions, pre-treatment performance status, pre-treatment weight loss, location of the primary tumor, tumor size, clinical and pathological stage, histology, tumor grade, treatment type (surgery, cytokine therapy, targeted therapy, chemotherapy, radiotherapy, and other therapy), local recurrence and distant metastasis (date of first recurrence/metastasis), current vital status (date of death and cause of death). The primary clinical endpoints were recurrence (including local recurrence and distant metastasis) and disease-specific survival. Time to recurrence/death was computed from date of surgery to date of last follow-up or recurrence/death.

Genotyping and imputation

Genotyping was performed in the Genotyping Core of MD Anderson Cancer Center using the Illumina HumanHap660W Beadchips and quality control for genotyping has been described previously [35]. Briefly, cases were excluded from analysis if they had genotyping call rates less than 95%, were found to be duplicated samples or known relatives to another sample, were found not to be of European ancestry, and were found to have reported a gender that did not match with X chromosome heterozygosity. We randomly selected 2% of the samples for duplicate genotyping. The concordance of SNP genotype calls was 99.2% for duplicated samples. Individual SNPs with minor allele frequen-

Table 1. Selected characteristics of the study patients

Characteristics	N (%)
Age, Mean (SD)	59.2 (10.6)
Sex	
Men	729 (67.1)
Women	357 (32.9)
Smoking status at diagnosis	
Never-smoker	491 (46.1)
Former smoker	428 (40.1)
Current smoker	147 (13.8)
BMI at diagnosis, kg/m^2	
<25	159 (19.9)
25-29.99 (overweight)	299 (37.5)
≥30 (obese)	339 (42.5)
Histology	
Clear Cell	839 (77.3)
Other	247 (22.7)
Clinical Stage	
I	399 (37.5)
II	81 (7.6)
III	292 (27.4)
IV	293 (27.5)
Fuhrman Grade	
2	358 (36.1)
3	421 (42.4)
4	214 (21.5)
Surgery	
Yes	992 (93.8)
No	66 (6.2)
Recurrence	
Yes	440 (40.5)
No	646 (59.5)
Survival status	
Dead	467 (43.0)
Alive	619 (57.0)

cy <1% and call rate <90% were excluded. Imputation was performed using the Michigan Imputation Server (https://imputationserver.sph.umich.edu/), an online server that generates phased and imputed genotypes using the Haplotype Reference Consortium (HRC Version r1.1) reference panels. The individual level data of the 10 LTL-associated SNPs were extracted from the genotyped and imputed dataset. Among these SNPs, four SNPs (rs10936599, rs2736100, rs9420907, and rs755017) were directly genotyped, and the other six were imputed with a high imputation accuracy (mean R^2) of 0.96.

Genetic risk scores (GRS) for LTL

A two-sample MR design was used to assess the associations between genetically predicted LTL and the risk of recurrence and death as described previously [29]. The SNP-LTL associations (estimate for each SNP in **Table 2**) were derived from published genome-wide association studies [24-26] and the SNP-RCC prognosis associations were estimated using individual genotype data in our patient cohort. Genetic risk scores (GRS) calculation for 10 telomere-length associated variants was used according to the following formula.

$$GRS_i = \sum_{j=1}^{10} w_j x_{ij}$$

Where GRS_i is the risk score for individual *i*. w_j is the weight or effect coefficient (estimate) for each SNP and x_{ij} (x_{ij}=0, 1 or 2) is the number of LTL increasing alleles for the *j*-th SNP. Weighted GRS assigned more weight to SNPs with stronger effects and many recent publications have utilized weighted GRS as an instrumental variable to estimate LTL and evaluated its associations with cancer risks and outcomes [27-34].

Statistical analysis

For each LTL-associated SNP, we evaluated its association with the risk of developing recurrence or death by calculating the hazard ratio (HR) and corresponding 95% confidence interval (95% CI) using multivariate Cox proportional hazards model, adjusting for age, smoking status, BMI, stage, grade, and treatment. To analyze the association between GRS and the risk of developing recurrence or death, we dichotomized GRS at the median value or categorized into four groups based on the quartile distribution, and used multivariate Cox proportional hazards model to calculate HR and corresponding 95% CI adjusting for age, smoking status, BMI, stage, grade, and treatment.

Results

Patient characteristics

Table 1 shows the distribution of selected characteristics of the 1,086 RCC patients. The mean age (standard deviation) at diagnosis was 59.2 (10.6) years. There were 729 men (67.1%) and 357 women (32.9%). The majority were never-smokers (45.2%) and former smokers (39.4%), with only 147 (13.5%) current smokers. About 80% of patients were obese

Table 2. The associations of individual LTL-associated SNPs with the risks of recurrence and death

SNP ID	Chr.	Position	Gene	Allele*	SNP-LTL		SNP-Recurrence			SNP-Death		
					EAF*	β*	β**	HR** (95% CI)	*P* value	β**	HR** (95% CI)	*P* value
rs11125529	2	54475866	ACYP2	A/C	0.14	0.07	-0.15	0.86 (0.69-1.08)	0.206	-0.14	0.87 (0.70-1.09)	0.222
rs6772228	3	58376019	PXK	T/A	0.94	0.04	-0.32	0.72 (0.52-1.02)	0.062	-0.02	0.98 (0.67-1.42)	0.901
rs10936599	3	169492101	TERC	C/T	0.75	0.10	-0.05	0.95 (0.81-1.12)	0.542	-0.16	0.85 (0.73-1.00)	0.047
rs7675998	4	164007820	NAF1	G/A	0.77	0.05	-0.16	0.85 (0.73-0.99)	0.043	-0.05	0.95 (0.81-1.12)	0.567
rs2736100	5	1286516	TERT	C/A	0.51	0.09	0.02	1.02 (0.89-1.17)	0.781	-0.02	0.98 (0.86-1.11)	0.724
rs9420907	10	105676465	OBFC1	C/A	0.13	0.14	-0.05	0.95 (0.78-1.15)	0.592	-0.16	0.85 (0.70-1.03)	0.101
rs3027234	17	8136092	CTC1	C/T	0.78	0.10	-0.09	0.91 (0.76-1.09)	0.316	-0.01	0.99 (0.84-1.18)	0.937
rs8105767	19	22215441	ZNF208	G/A	0.29	0.06	0.01	1.01 (0.88-1.17)	0.873	0.00	1.00 (0.87-1.15)	0.983
rs6028466	20	38129002	DHX35	A/G	0.06	0.06	-0.03	0.97 (0.73-1.29)	0.834	-0.02	0.98 (.075-1.29)	0.898
rs755017	20	62421622	ZBTB46	G/A	0.12	0.02	0.08	1.08 (0.89-1.31)	0.436	-0.10	0.91 (0.74-1.10)	0.321

*Alleles are short allele/long allele. Short alleles are used as the reference allele and long allele as effect allele. EAF: effect allele frequency; *β estimates of SNP-LTL association were from published GWAS; **β estimates for SNP-recurrence and SNP-Survival were from this study. **Adjusted by age, smoking status, BMI, histology, stage, grade, and treatment.

Table 3. GRS predictive of LTL is associated with recurrence in RCC patients

LTL	No Recurrence N (%)	Recurrence N (%)	Adjusted HR (95% CI)*	*P* value
Dichotomize				
Long	296 (61.28)	187 (38.72)	Reference	N/A
Short	275 (56.47)	212 (43.53)	1.26 (1.03-1.54)	0.025
Quartile				
4th (longest)	151 (63.18)	88 (36.82)	Reference	N/A
3rd	145 (59.43)	99 (40.57)	1.00 (0.74-1.35)	0.991
2nd	149 (61.32)	94 (38.68)	1.01 (0.75-1.36)	0.967
1st (shortest)	126 (51.64)	118 (48.36)	1.58 (1.19-2.11)	0.002
P for trend				0.002

*Adjusted by age, smoking status, BMI, histology, stage, grade, and treatment.

Table 4. GRS predictive of LTL is associated with survival in RCC patients

LTL	Alive N (%)	Dead N (%)	Adjusted HR (95% CI)*	*P* value
Dichotomize				
Long	291 (60.25)	192 (39.75)	Reference	N/A
Short	270 (55.44)	217 (44.56)	1.23 (1.00-1.50)	0.045
Quartile				
4th (longest)	151 (63.18)	88 (36.82)	Reference	N/A
3rd	140 (57.38)	104 (42.62)	1.18 (0.87-1.60)	0.280
2nd	139 (57.20)	104 (42.80)	1.24 (0.92-1.68)	0.157
1st (shortest)	131 (53.69)	113 (46.31)	1.45 (1.08-1.94)	0.012
P for trend				0.013

*Adjusted by age, smoking status, BMI, histology, stage, grade, and treatment.

(42.5%) and overweight (37.5%). The distribution of clinical stages was: 399 (37.5%) stage I, 81 (7.6%) stage II, 292 (27.4%) stage III, and 293 stage IV (27.5%). Over three quarters (77.3%) of patients had clear cell RCC. The vast majority (93.8%) of patients received surgical resection of tumors. A total of 440 (40.5%) patients developed recurrence and 467 (43.0%) patients died.

Associations of LTL-associated SNPs and GRS with prognosis of RCC

Table 2 shows the individual associations of 10 LTL-associated SNPs with recurrence and death. Patients carrying the effect allele (longer LTL) of rs7675998 in *NAF1* gene at chromosome 4 exhibited a significantly reduced risk of recurrence (HR=0.85, 95% CI, 0.73-0.99, P=0.043) and the effect allele (long LTL) allele of rs10936599 in *TERC* gene at chromosome 3 was associated with a significantly reduced risk of death (HR=0.85, 95% CI, 0.73-1.00, P=0.047).

We then constructed a weighted GRS to predict LTL for each patient using the formula described in the Methods. In multivariate Cox analysis adjusting for age, smoking status, BMI, histology, stage, grade, and treatment, lower GRS (shorter LTL) was associated with a significantly increased risk of recurrence (HR=1.32 per SD decrease, 95% CI, 1.02-1.70, P=0.032). When patients were dichotomized into low and high GRS groups based on the median (50th percentile) value of GRS, patients with low GRS (short LTL) had a 1.26-fold (95% CI, 1.03-1.54, P=0.025) increased risk of recurrence compared to those with high GRS (long LTL). When patients were categorized into four groups based on the quartile distribution of GRS, patients with the lowest quartile of GRS (shortest quartile of LTL) were 58% more likely to develop recurrence than those with the highest quartile of GRS (longest quartile of LTL) (HR=1.58, 95% CI, 1.19-2.11 P=0.0016) (**Table 3**).

Likewise, patients with lower GRS (shorter LTL) had a significantly increased risk of death (HR=1.46 per SD decrease, 95% CI, 1.13-1.88, P=0.0038). When patients were dichotomized into low and high GRS groups based on the median value of GRS, patients with low GRS exhibited a 1.23-fold (95% CI, 1.00-1.50, P=0.045) increased risk of death compared to those with high GRS. When patients were categorized into four groups based on the quartile distribution of GRS, the HRs for patients with the lowest quartile of GRS, 2nd quartile, and 3rd quartile of GRS were 1.45 (95% CI, 1.08-1.94, P=0.012), 1.24 (95% CI, 0.92-1.67, P=0.157), and 1.18 (95% CI, 0.87-1.60, P=0.280), respectively (P for trend =0.013), compared to patients with the highest quartile of GRS (**Table 4**).

Discussion

In this study, we applied an MR approach to show that genetically predicted short LTL was an independent predictor of worse prognosis in RCC patients. To our knowledge, this is the first study to evaluate the associations of LTL with the recurrence of RCC and the first one to use MR approach for studying LTL and RCC survival.

Telomeres play a key role in maintaining genomic integrity via protecting chromosomes from degradation, end-to-end fusion, and abnormal recombination [36]. Numerous observational studies have assessed the associations of LTL with the risk of cancers, including RCC [16, 18, 37-41]. Earlier small hospital-based retrospective case control studies reported that short LTL associated with higher risks of RCC [38, 39], which was likely spurious association due to reverse causation, an inherited limitation when evaluating an intermediate biomarker like LTL and cancer risks [37, 42]. Two prospective cohort studies did not find significant associations between pre-diagnostic LTL and RCC risks [16, 41]. In terms of LTL and RCC outcome, an early small study of 105 RCC patients with 28 cancer-specific death found long LTL was associated with an increased risk of cancer-specific death [43]. A recent large study investigated LTL and RCC-specific survival among 684 cases from a population-based U.S. kidney cancer study (USKC) and 241 cases from the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) and found short LTL was associated with poorer disease-specific survival in both USKC (lowest vs highest quartile: HR: 2.3, 95% CI: 1.2-4.4) and PLCO (HR: 2.4, 95% CI: 1.0-5.4) [19]. No study has specifically evaluated the role of LTL in RCC recurrence. Short LTL has been associated with poor survival in several other cancers [29, 30, 34, 44-47], but a few studies also reported that long LTL was associated with poor prognosis [48-50]. The heterogeneous results between LTL and cancer prognosis may be due to different cancer types, heterogeneous patient population, small sample sizes of most studies, and technical variability. The reproducibility of the popular real-time quantitative PCR technique to measure LTL in human population studies is profoundly impacted by many pre-analytic and analytical factors (e.g., DNA extraction method, storage, and assay conditions) [51-53].

MR study uses genetic variants as a proxy for a risk factor/intermediate biomarker [20-23]. MR study is not susceptible to unmeasured confounding factors and reverse causation typical of retrospective observational studies. In addition, genotyping technology is robust without technical variations. MR study has been increasingly applied in population studies for assessing exposures/biomarkers and disease risks and outcomes and LTL is one of the most commonly studied biomarkers using MR approach [20-22, 27-34]. Two recent large MR studies reported significant associations between longer LTL and increased risks of RCC [21, 27]. Our study is the first to use an MR approach to assess the associations of genetically predicted LTL with RCC recurrence or survival. Consistent with the results of aforementioned observational studies of USKC and PLCO patient populations [19], we found genetically predicted short LTL was associated with a significantly increased risk of death in RCC patients, and for the first time, we also found a significant association between short LTL and recurrence. Our study provided strong evidence for a causal relationship between short LTL and poor RCC prognosis.

The biological mechanisms underlying the associations between short LTL and poor RCC prognosis may lie in two aspects. First, LTL serves as a surrogate for tissue telomere length and short LTL indicates short telomere length in kidney tissues. Numerous studies have shown that somatic telomere shortening increases genomic instability and promote carcinogenesis in mice models [54-58]. In human studies, a high correlation was observed between telomere length in blood and other tissues among newborns and adults [11, 13]. Telomere shortening and telomerase activation were associated with RCC progression and aggressive RCC [59-62]. Therefore, short LTL is a surrogate for short telomeres in kidney tissues, which is a poor prognostic factor. Second, LTL reflects the homeostasis of immune cells and short LTL may therefore indicate increased senescence of immune cells and weakened immunity. In this regard, the peripheral blood leukocytes of colorectal patients with short LTL had higher proportion of CD4(+) T cell and lower proportion of B cell, as well as lower concentration of plasma transforming growth factor-β1, indicating weakened immune response [44]. Similar observations were made in gastric can-

cer patients and those with short LTL had an enhanced immunosuppressive status [45]. Therefore, both local and systemic mechanisms may contribute to the observed associations between short LTL and poor prognosis of RCC.

There are both strengths and limitations for our study. This is the first study to report a significant association between short LTL and an increased risk of recurrence in RCC patients. This is also the first MR study of LTL in RCC prognosis. The findings were consistent with a prior observational study [19]. The sample size was large and all the patients were treated at a single institution with consistent treatment and long-term follow-up. In terms of limitations, first, like other MR studies using SNPs as instrument variables, the SNPs used in this study only explain approximately 2% of the variability of LTL. Additional SNPs are desired to enhance instrument strength. Nevertheless, many recent high-impact studies have clearly demonstrated the power of using these SNPs as proxy to assess genetically predicted LTL and various diseases [20-22, 27-34, 63-66]. Second, we only included patients of European ancestry in our analysis due to the small number of minority patients. Future studies are needed to assess the associations of LTL with RCC prognosis in other racial/ethnic groups.

In conclusion, using a Mendelian randomization approach, we found that short LTL is associated with increased risks of recurrence and death for RCC patients of European ancestry. Short LTL may become a biomarker of poor prognosis and facilitate the risk stratification of RCC patients for better-informed clinical management.

Acknowledgements

This study was financially supported by an MD Anderson Cancer Center start-up fund. The funder did not play a role in the design and execution of this study and the writing of the manuscript.

Disclosure of conflict of interest

None.

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