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Original Article

Patients with benign prostatic hyperplasia show shorter leukocyte telomere length but no association with telomerase gene polymorphisms in Han Chinese males

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Abstract: Objective: Benign prostatic hyperplasia (BPH) is an age-related disease, occurring in >70% of men of age >60. Because telomeres and telomerase play a key role in aging and age-related diseases, and certain telomerase gene single nucleotide polymorphisms (SNPs) are shown to be associated with the susceptibility to age-related diseases, we wanted to determine the relationship between BPH and leukocyte telomere length (LTL) and telomere length-related single nucleotide polymorphisms (SNPs) of the telomerase holoenzyme genes. Methods: Peripheral blood was collected from both BPH patients and age-matched healthy male controls and genomic DNA was extracted. rs2736100 and rs2736098 at the *TERT* and rs12696304 at the *TERC* locus were analysed using pre-designed TaqMan SNP genotyping assay kits. LTL was determined using qPCR. Results: Patients with BPH had significantly shorter LTL (1.231 ± 0.532 vs 0.899 ± 0.322, $P < 0.001$). The genotyping results show similar frequencies in rs2736100, rs2736098 and rs12696304 between healthy and BPH individuals. Conclusions: Shorter telomeres but not telomerase SNPs at the TERT and TERC loci, are associated with BPH. Short telomeres may promote senescence of a fraction of prostatic epithelial cells, while senescent cells in turn facilitate epithelial and stromal cell proliferation by the senescence-associated secretory phenotype mechanism, thereby eventually leading to BPH development.

Keywords: BPH, SNP, TERC, TERT, telomere

Introduction

Benign prostatic hyperplasia (BPH) is a chronic disease with an increased volume of transition zone resulting from proliferation of both epithelial and stromal cells in the prostate, and occurs most commonly in old men [1-3]. BPH frequently causes lower urinary tract symptoms, thereby affecting patients' life-quality [1, 2, 4]. To better develop strategies for BPH prevention and intervention, scientists and urologists have made great efforts in exploring the pathogenesis of BPH. The accumulated evidence suggests that androgen/androgen receptor (AR), obesity or metabolic syndrome, genetic background, and many other factors are involved in BPH development [2, 4-7]. A recent study showed that heritability accounted for 40.48% of BPH cases [8]. However, the exact mechanism(s) remain incompletely understood.

Human linear chromosomes terminate with TTAGGG repeat sequences, a so-called telomere, and these telomeric repeats together with telomere-associated proteins form a protective cap essential for genomic stability and integrity [9, 10]. Telomeres are elongated by telomerase, an RNA-dependent DNA polymerase with telomerase reverse transcriptase (TERT) and telomerase RNA template (TERC) as its core components [9, 11]. Differentiated human cells in general lack telomerase activity, which, together with "the end-replication problem", results in progressive telomere shortening with cellular division [9, 10, 12]. When the

telomere becomes too short (dysfunctional) to protect chromosomes, the DNA damage response is activated, thereby triggering permanent growth arrest of cells designated replicative senescence [9, 13]. Thus, telomere erosion serves as a mitotic O'clock recording the number of cell divisions and limiting their lifespan, and is widely accepted as a biomarker for aging and age-related conditions [9, 13-16]. Indeed, short leukocyte telomere length (LTL) has been shown to be associated with cancer, cardiovascular diseases, stroke, diabetes, increased mortality and other age-related disorders [9, 14, 15, 17-20]. However, despite the fact that BPH is almost exclusively seen in old men, little is known about telomere biology in BPH.

Multiple single nucleotide polymorphisms (SNPs) are present in the *telomerase* genes and some of these SNPs are highly associated with LTL in general populations, and risk of diseases as described above [15, 21-28]. A number of SNPs at the *TERT* locus are associated with prostate cancer susceptibility, as described in many publications, but only one report showed a correlation of BPH with rs2736098 [29]. It is currently unclear whether other SNPs at the *TERT* and *TERC* loci are associated with BPH susceptibility.

In the present study, we thus sought to determine whether telomere length and LTL-related SNPs, contribute to susceptibility to primary BPH.

Materials and methods

Study populations

The case-control individuals include 322 healthy controls and 490 primary BPH patients. They were all Han Chinese and recruited from the Health Examination Center at Shandong University Second Hospital between Dec. 2016 and Mar. 2018. Primary BPH was diagnosed when the prostate gland volume is >24 cm^3, as determined using Brightness-mode Ultrasound and other secondary factors are excluded. Genotyping was performed in all the controls and patients, while telomere length assessment was done in all the control and 399 patients due to insufficient DNA. The study was approved by the Ethics Review Committee of Shandong University Second Hospital and the informed consent was obtained from all participants.

DNA extraction and leukocyte telomere length (LTL) assay

Genomic DNA was extracted from peripheral blood cells using TIANGEN DNA extraction kits. Genomic DNA was isolated from peripheral blood cells as above and LTL was assessed using real-time PCR as previously described [14, 17, 30]. Briefly, 2 ng of DNA were used for each PCR reaction. The primer sequences for human telomere (Tel 1b and Tel 2b) and β-globin (HBG3 and HBG4) were: Tel1b: 5'-CGGTTTG-TTTGGGTTTGGGT-TTGGGTTTGGGTTTGGGTT-3'; Tel2b: 5'-GGCTTGCCTTACCCTTACCCTTACCC-TT-ACCCTTACCCT-3'; HBG3: 5'-TGTGCTGGCCCAT-CACTTTG-3', and HBG4: 5'-ACCAGCCA-CCACTT-TCTGATAGG-3'. T/HBG values were determined using the formula $T/S = 2^{-\Delta Ct}$, where ΔCt = average $Ct_{telomere}$ - average $Ct_{\beta\text{-globin}}$. The T/S ratio was arbitrarily expressed as LTL. Age-adjusted LTL for each control and patient was done by subtracting the subject's linear predicted LTL from the observed one.

Genotyping of the TERC rs12696304, and TERT rs2736100 and rs2736098 variants

The *TERC* rs12696304 (C/G), and *TERT* rs-2736100 (A/C) and rs2736098 (A/G) genotyping was performed using pre-designed TaqMan SNP genotyping assay kits on an ABI 7500 Life Tech (Applied Biosystems), as described [31]. Both positive and negative controls were included in all assays and the running conditions were: 95°C for 5 min, followed by 40 cycles of 92°C for 15 s and 60°C for 30 s.

Statistical analyses

Differences in age, BMI, cholesterol, TG, LDL, HDL, and LTL between patients and healthy controls was assessed using Student's t-test. The evaluation of distribution differences of selected variables and alleles of the *TERC* rs12696304 and *TERT* rs2736100/rs2736098 between BPH patients and healthy controls was done using χ^2 test. Hardy-Weinberg equilibrium of the genotype distribution among the controls and cases was tested by a goodness-of-fit χ^2 test. Unconditional univariate and multivariate logistic regression analyses were used to estimate ORs for risk of BPH and their 95%

Table 1. Summary of age, BMI, and metabolic variables in controls and BPH patients

	Control (N)	BPH (N)	*P* value
N (Total)	322	490	
Age (years)	51.4 ± 8.2 (322)	52.3 ± 8.0 (490)	0.123
Body mass index (BMI)	26.4 ± 3.4 (304)	26.3 ± 3.3 (400)	0.867
Cholesterol	5.14 ± 0.94 (304)	4.88 ± 0.91 (400)	< 0.001
Triglycerides	1.70 ± 1.05 (304)	1.48 ± 0.85 (400)	0.004
Low density lipoprotein	2.67 ± 0.75 (195)	2.76 ± 0.69 (208)	0.251

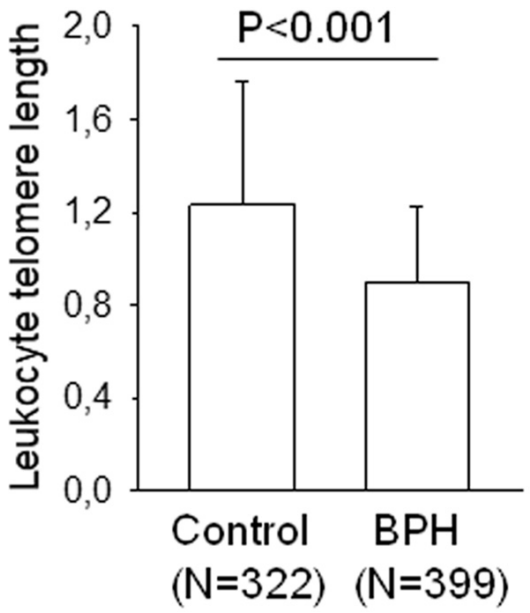

Figure 1. Shorter leukocyte telomere length (LTL) in patients with benign prostatic hyperplasia (BPH). LTL was determined in both age-matched control males (N=322) and BPH patients (N=390) using qPCR.

confidence intervals (CIs). All the tests were computed using SPSS17.0 software. *P* values of <0.05 were considered significant.

Results

Characteristics of study subjects

A total of 490 patients with primary BPH and 322 healthy males were included in the present study. Patient and control ages are shown in **Table 1**. Because obesity or metabolic syndrome (MetS) has been shown to be associated with both BPH development and telomere length, we first compared the difference in BMI and serum lipid variables between controls and patients. Both patients and controls had similar BMI and LDL, while significantly lower levels of serum cholesterol and TG were observed in patients (**Table 1**).

Shorter LTL in patients with BPH

LTL was assessed in both controls (322) and BPH patients (399) using qPCR. LTL was 1.231 ± 0.532 and 0.899 ± 0.322 for controls and patients, respectively, which differed significantly ($P < 0.001$) between the control and patient groups (**Figure 1**).

No association between the rs12696304/ rs2736098/rs2736100 genotypes and susceptibility to BPH

Given the finding above, we sought to determine whether shorter LTL in BPH patients was due to differences in the SNPs at TERC and TERT alleles, or whether these SNPs confers BPH risk. For these purposes, we chose three SNPs (TERC rs12696304 and TERT rs2736098 and rs2736100) that have been shown to be involved in the telomere length control. Genotyping results, summarized in **Table 2**, showed largely similar distribution frequencies of all three SNPs in the patient group compared to those of controls. There were no differences in LTL among different genotypes of these three SNPs (data not shown).

Discussion

BPH is an age-related disease [1, 2, 4]. In early reports, two independent groups observed the accumulation of senescent cells in BPH tissues, and the more senescent cells were present in prostate, the more severe BPH was [32, 33]. Cellular senescence can be induced by different intrinsic or extrinsic factors, but telomere shortening or dysfunction is a key underlying mechanism in the aged population [9, 10, 14, 34]. In the present study, we demonstrated a significantly shortened LTL in BPH patients than age-matched healthy males. It is known that LTL and its shortening rate are very similar to those in other tissues/organs in the same individual under physiologic conditions [34].

Table 2. Summary of rs2736100, rs2736098 and rs12696304 genotypes in controls and BPH patients

	Control	BPH	Odds ratio (95% CI)	*P* value
N	322	490		
Genotypes				
rs2736100 (N)	322 (100%)	490 (100%)		
AA	121 (37.6)	179 (36.5)	1.0 (ref.)	
AC	159 (49.4)	227 (46.3)	0.965 (0.710-1.312)	0.82
CC	42 (13.0)	84 (17.2)	1.352 (0.874-2.092)	0.175
AC + CC	201	311	1.046 (0.782-1.399)	0.762
A	401 (62.3)	585 (59.7)		
C	243 (37.7)	395 (40.3)	0.897 (0.732-1.101)	0.299
rs2736098 (N)	321 (100%)	487 (100%)		
CC	135 (42.2)	211 (43.3)	1.0 (ref.)	
CT	154 (47.8)	214 (44.0)	0.889 (0.659-1.199)	0.441
TT	32 (10.0)	62 (12.7)	1.240 (0.768-2.000)	0.378
CT + TT	186	276	0.949 (0.714-1.262)	0.721
C	424 (66.0)	636 (65.0)		
T	218 (34.0)	338 (35.0)	1.034 (0.838-1.275)	0.757
rs12696304 (N)	321 (100%)	487 (100%)		
GG	164 (51.1)	242 (49.7)	1.0 (ref.)	
GC	139 (43.3)	207 (42.5)	1.009 (0.753-1.352)	0.951
CC	18 (5.6)	38 (7.8)	1.431 (0.789-2.593)	0.236
GC + CC	157	245	1.058 (0.798 1.402)	0.697
G	467 (72.7)	691 (70.9)		
C	175 (27.3)	283 (29.1)	1.093 (0.875-1.365)	0.433

BPH: Benign prostatic hyperplasia.

Therefore, our finding, together with the observation by Castro, et al and Choi, et al, strongly suggests a role for telomere shortening-mediated senescence in the pathogenesis of BPH.

Numerous observations have shown that the presence of shorter telomeres is a feature of many age-related conditions and diseases including immunosenescence, cardiovascular disease, stroke, cancer, sarcopenia, osteoporosis, osteoarthritis, and skin aging [14, 19]. Here we add BPH to this list. As described above, very short telomere triggers cell senescence, and one of the key features for senescent cells is the senescence-associated secretory phenotype (SASP) [35]. The components of SASP include growth factors, enzymes and cytokines such as IL-1, IL-6, IL-8, and others [35]. Senescent prostatic epithelial cells express high levels of IL-1α, thereby inducing FGF7 secretion and proliferation of non-senescent epithelial cells [32, 33]. In addition, increased stromal proliferation also occurs in BPH, which resulted from markedly increased FGF2 generation mediated by senescent prostatic epithelial cell-derived IL-8 [36].

It is currently unclear which mechanisms control an individual's telomere length. Genome-wide association studies and other molecular biologic approaches have mapped LTL-associated SNPs to genetic loci in the general population, the majority of which harbor LTL maintenance genes such as rs2736098, rs2736100 and rs12696304 [15, 20, 25, 27, 37]. However, we failed to see an association between these SNPs and LTL in both controls and BPH patients, indicating that other factors contribute to shorter LTL occurring in BPH patients. In addition, no correlation was observed between BPH susceptibility and these three SNPs, which is contrast to an earlier report showing rs2736098-A allele-mediated BPH risk [29]. We notice that Caucasian patients were recruited in that study, while our cohort exclusively included Han Chinese controls and PBH patients. There is a

significant difference in the rs2736098, rs2736100 and rs12696304 genotypes between Han Chinese and European Caucasians [18], which may provide a putative explanation for such a discrepancy. Indeed, racial or ethnic disparities in disease incidence and pathogenesis have been well documented, and different genetic backgrounds and genetic variants are believed to play important parts.

MetS including obesity, diabetes, and dyslipidemia has been revealed as a risk factor for BPH [5], while these variables are also associated with shorter LTL in the general population [20, 38, 39], which raises the question of whether the observed shorter LTL in BPH is secondary. To elucidate this scenario, we compared BMI and blood lipid concentrations between controls and patients. BMIs were very similar to each other, but unexpectedly, the patient group had significantly lower levels of cholesterol and LDL than did healthy controls. Collectively, there may exist a causal relationship between shorter LTL and BPH.

Shorter LTL has been shown to be associated with cancer risk. In malignant cells/tissues including prostate cancer, telomeres are in general shorter than in adjacent normal ones and telomerase is frequently activated [40]. Similarly, widespread telomere dysfunction has been observed in BPH [41], and more intriguingly, Rane et al found that stem/progenitor cells derived from BPH tissues expressed high levels of TERT, TERC and telomerase activity [42]. These results suggest that BPH may mimic cancer-related telomerase activation to stabilize telomere for cellular expansion. Therefore, targeting telomerase is suggested as a strategy for BPH therapy.

In summary, the findings presented herein show that shorter LTL is significantly associated with BPH in the Han Chinese males, which provides insight into BPH pathogenesis. Probably, short telomere promotes senescence of a fraction of prostatic epithelial cells, while senescent cells in turn facilitate epithelial and stromal cell proliferation through a SASP mechanism.

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Disclosure of conflict of interest

None.

Abbreviations

AR, androgen receptor; BPH, Benign prostatic hyperplasia; LTL, leukocyte telomere length; SASP, senescence-associated secretory phenotype; SNP, Single nucleotide polymorphism; TERC, telomerase RNA component; TERT, telomerase reverse transcriptase.

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