Circulating leukocyte telomere length and risk of overall and aggressive prostate cancer

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Background: Recent large-scale prospective studies suggest that long telomeres are associated with an increase cancer risk, counter to conventional wisdom.

Methods: To further clarify the association between leukocyte telomere length (LTL) and prostate cancer, and assess genetic variability in relation to both LTL and prostate cancer, we performed a nested case–control study (922 cases and 935 controls). The participants provided blood in 1993–1995 and were followed through August 2004 (prostate cancer incidence) or until 28 February 2013 (lethal or fatal prostate cancer). Relative LTL was measured by quantitative PCR and was calculated as the ratio of telomere repeat copy number to a single gene (36B4) copy number (T/S). Genotyping was performed using the TaqMan OpenArray SNP Genotyping Platform. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of all prostate cancer and subtypes defined by Gleason grade, stage and lethality (metastasis or death).

Results: We observed a positive association between each s.d. increase in LTL and all (multivariable-adjusted OR 1.11, 95% CI: 1.01–1.22), low-grade (OR 1.13, 95% CI:1.01–1.27), and localised (OR 1.12, 95% CI:1.01–1.24) prostate cancer. Associations for other subtypes were similar, but did not reach statistical significance. In subgroup analyses, associations for high grade and advanced stage (OR = 2.04, 95% CI 1.00–4.17; P interaction = 0.06) or lethal disease (OR = 2.37, 95% CI 1.19–4.72; P interaction = 0.01) were stronger in men with a family history of the disease compared with those without. The minor allele of SNP, rs7726159, which has previously been shown to be positively associated with LTL, showed an inverse association with all prostate cancer risk after correction for multiple testing (P = 0.0005).

Conclusion: In this prospective study, longer LTL was modestly associated with higher risk of prostate cancer. A stronger association for more aggressive cancer in men with a family history of the disease needs to be confirmed in larger studies.

Several studies have examined leukocyte telomere length (LTL) in relation to cancers, but with contrasting results (Hou et al., 2012). Initially, shorter telomeres were believed to be associated with an increase in cancer risk, but recent large-scale prospective studies have observed null associations (De Vivo et al., 2009; Weischer et al., 2013) or showed that long telomeres are associated with an
increased risk in cancer (Shen et al, 2011; Hou et al, 2012; Lan et al, 2013; Lynch et al, 2013). One prospective study on LTL and colorectal cancer observed a u-shaped association (Cui et al, 2012). Recently, Gu and Wu (2013) proposed that this inconsistency may be in part because the effect of LTL varies by specific cancer type. Another potential explanation is that non-prospective case–control studies were subject to reverse causation in which tumour carcinogenesis affected telomere length. In a meta-analysis stratified by study design, Wenzensen et al (2011) observed that increased risk in cancer associated with short telomeres was mainly driven by case–control studies (odds ratio (OR) in pooled analysis = 1.96; OR in case–control studies = 2.9; OR in prospective studies = 1.16), suggesting that telomere shortening occurs mainly after diagnosis, and therefore, might not be of value in cancer risk prediction (Pooley et al, 2010). Indirect evidence that both short and long LTL may contribute to the development of specific cancers comes from a recent genome wide association study (GWAS) that identified loci associated with LTL (Codd et al, 2013) and assessed their association with different cancer types. The authors found that alleles associated with LTL showed associations with specific cancers in both directions (Codd et al, 2013).

Currently, only two prospective studies have investigated circulating LTL and prostate cancer. In a nested case–control study in the Prostate, Lung, Colon and Ovarian Cancer Screening Trial (PLCO), men with shorter telomeres appeared to have a lower risk of advanced prostate cancer (OR = 0.81, 95% confidence interval (CI) 0.64–1.02, comparing the lowest quartile with the highest) (Mirabello et al, 2009). A Danish population-based cohort study of 47,102 individuals indicated an inverse association between shorter telomeres and prostate cancer incidence (hazard ratio (HR) = 0.94, 95% CI 0.85–1.04, cases n = 418), but not fatal prostate cancer (HR = 1.04, 95% CI 0.87–1.25; deaths n = 157) (Weischer et al, 2013).

In genetic studies, the telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC) genes, together comprising the most important unit of the telomerase complex, were identified as risk loci for prostate cancer (Rafnar et al, 2009; Kote-Jarai et al, 2011; Kote-Jarai et al, 2013). Variants in these genes have been associated with LTL in recent GWAS (Codd et al, 2010; Bojesen et al, 2013; Codd et al, 2013; Pooley et al, 2013). The mechanisms that link LTL with cancer is much more complex than the oversimplified view presented so far. To further clarify the association between LTL and risk of all prostate cancer as well as subtypes defined by Gleason grade, stage and progression, we performed a case–control study of 922 cases and 935 controls nested within the prospective Health Professionals Follow-up Study (HPFS). In addition, we evaluated the association of variation in genes related to telomere length as well as prostate cancer with both prostate cancer risk and telomere length.

**Materials and Methods**

**Study population.** We ascertained incident prostate cancer cases and sampled controls from participants in the HPFS, a prospective cohort study of 51,529 US men aged 40–75 years who enrolled in 1986 (https://www.hsp.harvard.edu/hfps). The men filled out mailed surveys on their demographics, lifestyle, and medical history at baseline and during follow-up every 2 years, and on their diet at baseline and every 4 years. Deaths in the participants are confirmed by medical record review. Study investigators reviewed medical and pathology records to extract data on stage (TNM staging system) at diagnosis and histological grade, assessed using Gleason scores. We used pathological stage and grade when available and clinical measures if pathological information was not available. Deaths were identified via repeated mailings, telephone calls, and searches of the National Death Index. Causes of deaths were confirmed through review of medical records and death certificates. Biennial follow-up surveys were mailed to those who reported prostate cancer to collect information on disease progression (e.g., metastases). We identified 922 eligible prostate cancer cases between the dates of blood draw through August 2004. Follow-up for progression to prostate cancer-specific death was complete through 28 February 2013; 96.1% of the prostate cancer cases were confirmed by medical record review.

In the original nested case–control design, for each case, we sampled a control that was alive and had not been diagnosed with cancer up to the date of the case’s diagnosis. The cases and controls were matched on year of birth, ever having had a PSA test before the date of providing the blood sample, and the time of day, season, and year that the blood sample was provided. To be eligible, controls were required to have had a PSA test after the date they provided a blood sample.

The Human Subjects Committee of the Harvard School of Public Health approved the HPFS, and written informed consent was obtained from all participants. Both the Human Subjects Committee of the Harvard School of Public Health and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health approved the study on telomeres, genetic variability and prostate cancer.

**Telomere length determination.** Genomic DNA was extracted from peripheral blood leukocytes using the QIAmp 96-spin blood protocol (Qiagen, Chatsworth, CA, USA). Pico-Green quantification of genomic DNA was performed using a Molecular Devices 96-well spectrophotometer (Sunnyvale, CA, USA). Relative LTL was determined using a modified, high-throughput version of the quantitative PCR (qPCR)-based telomere assay (Cawthon, 2002; Wang et al, 2008). The qPCR telomere assay was run on Applied Biosystems 7900HT Sequence Detection System (Foster City, CA, USA). Laboratory personnel were blinded to participant characteristics and all assays were processed in triplicates by the same technician, and under identical conditions. The average relative LTL was calculated as the ratio of telomere repeat copy number to a single gene (36B4) copy number (T/S). Relative LTL is reported as the exponentiated T/S ratio corrected for a reference sample. The telomere and single-gene assay coefficients of variation (CVs) for triplicates were <0.8%. The CV for the mean exponential T/S ratio was 16.0%. Although this assay provides a relative measurement of telomere length, T/S ratios highly correlate with absolute telomere lengths determined by southern blot (r = 0.82; P < 0.001) (Cawthon, 2002).

**Covariate assessment.** We used information from the 1994 questionnaire or, if not available, the most recent before 1994 to calculate body mass index (BMI), smoking amount (indicated by pack-years), alcohol consumption (indicated by grams of ethanol) and vigorous physical activity (indicated by metabolic equivalent (MET) per week) as close to time of blood donation (1993–1995, with the majority donating blood in 1994) as possible.
Single-nucleotide polymorphism (SNP) selection and genotyping. The main aim was to evaluate SNPs previously related to telomere length, but we also included SNPs that have been related to prostate cancer risk if they were located in or close to telomere maintenance genes (TERT or TERC). We identified 32 SNPs from GWA (Rafnar et al, 2009; Codd et al, 2010; Levy et al, 2010; Kote-Jarai et al, 2011; Prescott et al, 2011; Mangino et al, 2012; Bojesen et al, 2013; Codd et al, 2013; Pooley et al, 2013) or fine mapping studies (Kote-Jarai et al, 2013) that had minor allele frequencies > 5% in whites. For SNPs that were in linkage disequilibrium with $R^2 > 0.80$, we selected the SNP with the stronger association from the literature. We were able to genotype 22 SNPs (see Supplementary Table 1), but 1 failed genotyping (rs6772228). Blood samples from matched case–control pairs were handled identically and assayed in the same batch in a blinded fashion. Genotyping was performed at the Dana Farber/Harvard Cancer Center High-Throughput Genotyping Core using the TaqMan OpenArray SNP Genotyping Platform (Applied Biosystems) according to the manufacturer’s instructions. To validate genotyping procedures, 10% blinded quality control samples were inserted. All SNPs had >90% genotype completion, and the concordance was 100% for blinded quality control samples.

Statistical analysis. The final sample size consisted of 922 cases and 935 controls, after removal of failed qPCR samples (25%). To preserve sample size, we included all cases and controls in the analysis irrespective of whether the matched pair was present. We used unconditional logistic regression to estimate ORs and 95% CIs of prostate cancer, adjusting for age at blood draw (continuous, years) and matching factors (age at selection (continuous, years), PSA test before blood collection (yes/no/unknown) and year of blood collection). We did not adjust for the time of day and season that the blood sample was provided because these factors were not related to telomere length. In a second model, we additionally adjusted for smoking (0, 0.1–20, 20.1–40, > 40 pack-years), BMI (< 25, ≥25–29.9, ≥ 30–34.9, ≥ 35 kg m$^{-2}$), and vigorous physical activity (quartiles, MET-hours per week), since these factors have been associated with telomere length as well as prostate cancer (Giovannucci and Michaud, 2007; Mirabello et al, 2009). We also estimated the ORs of (a) low grade ($n = 461$; Gleason sum ≤ 7), (b) Gleason sum = 7 ($n = 307$), (c) high grade ($n = 90$; Gleason sum > 7), (d) lethal disease ($n = 81$; death by prostate cancer or metastasis in bone or other organs, except lymph nodes), (e) localised disease ($n = 774$; TNM stage T1b, T2b, T3a, and N0M0) and (f) advanced stage or lethal disease ($n = 103$) (> T3b, N +, or M + at diagnosis or progression to metastasis or prostate cancer death during follow-up).

We modelled LTL in two ways: (1) using indicator variables for quartiles of relative LTL with cut points based on the distribution among the controls and (2) using LTL as a continuous measure (per s.d.). We assessed effect modification by age at blood draw (dichotomised by the median; ≤ 64 or > 64 years), cigarette smoking status (ever, never) in 1994 and family history of prostate cancer (yes/no). We present stratified effect estimates by each of these characteristics. We also assessed whether telomere length was associated with early-onset prostate cancer (< age 65). The statistical significance of the interaction was assessed using a Wald test for the multiplicative interaction term of each of the characteristics and LTL (modelled continuously).

The additive genetic model was used for the SNP analyses, which assumes that the effect of the heterozygous genotype is intermediate between the two homozygous genotypes. The homozygous genotype of the major allele was coded as 0. Age-adjusted (age at blood draw) unconditional logistic regression between each individual SNP and prostate cancer or low and high LTL (dichotomised at the median) was performed and $P$-values were Bonferroni corrected, considering 21 independent tests. All $P$-values were two sided and analyses were conducted using SAS release 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Cases and controls were similar on demographic and lifestyle factors (Table 1). The mean age at prostate cancer diagnosis was 69.5 years and the mean time between blood draw and diagnosis was 5.5 years. As expected, a statistically significant inverse correlation was found between relative telomere length and age at blood draw ($r = -0.19, P < 0.0001$) in controls.

Leukocyte telomere length was not associated with all prostate cancer or any of the subtypes when comparing quartiles of LTL; neither in models adjusting for the matching factors or when additionally adjusting for BMI, smoking and physical activity (Table 2). When telomere length was modelled continuously, however, longer telomeres were modestly positively associated with all prostate cancer ($P = 0.03$), low-grade ($P = 0.04$) and localised ($P = 0.03$; Table 2) prostate cancer. Per each s.d. increase in telomere length, the OR was 1.11 for all prostate cancer, 1.13 for low-grade disease and 1.12 for localised disease. Results were similar for intermediate grade, high-grade, advanced and lethal disease, but the estimates were not statistically significant. Of note, 28 cases were overlapping between the high-grade ($n = 90$) and the advanced stage or lethal disease ($n = 103$) groups. With that in mind, these two outcomes should not be considered completely independent results.

As presented in Table 3, there was some evidence that men with a family history of prostate cancer had an increase in risk of...
In this prospective study, we found that longer circulating LTL was associated with a higher risk of prostate cancer. Longer telomere length was associated with a higher risk of high-grade, advanced stage or lethal disease in men with a family history of prostate cancer. The minor allele of SNP rs7726159 in the TERT gene showed a statistically significant inverse association with prostate cancer, but there was no evidence that this SNP was associated with telomere length in our study.

Telomeres are repetitive DNA sequences (TTAGGG) that protect the ends of linear chromosomes. In adult somatic cells telomeres shorten over time because standard DNA polymerase cannot replicate them during cell division, a phenomenon called the end-replication problem. The epidemiological evidence for associations between circulating LTL and cancer has been equivocal. Some studies support the hypothesis that shorter circulating LTL is associated with higher cancer risk (Wentzensen et al., 2011; Hou et al., 2012), although the associations tend to be stronger in retrospective studies and may differ by cancer type (Gu and Wu, 2013). In prospective studies, long telomeres have been associated with an increased risk of several cancers such as melanoma (Han et al., 2009), lung cancer (Shen et al., 2011), non-Hodgkin lymphoma (Lan et al., 2013) and pancreatic cancer (Lynch et al., 2013). There are plausible explanations also for a positive association between LTL and cancer. As short telomeres may induce cellular senescence, long telomeres are generally a marker for actively reproducing cells that are at higher risk of obtaining tumour-causing mutations (Jones et al., 2012). The importance of balance between elongation (by the telomerase enzyme) and telomere shortening to maintain a stable, ‘optimal’ length for cell cycle control has also been suggested (Ducray et al., 1999). For an accurate comparison between studies,

### Table 2. Odds ratios (95% confidence intervals) for prostate cancer and subtypes by quartiles of leukocyte telomere length

| Outcome                        | Ca/Co OR (95% CI) | Ca/Co OR (95% CI) | Ca/Co OR (95% CI) | Ca/Co OR (95% CI) | OR (95% CI) per s.d. | P    |
|--------------------------------|-------------------|-------------------|-------------------|-------------------|---------------------|------|
| Total prostate cancer          |                   |                   |                   |                   |                     |      |
| Model 1*                       | 215/228           | 1.00 (ref.)       | 205/235           | 0.93 (0.71, 1.21) | 247/242             | 1.09 (0.84, 1.41) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 1.00 (ref.)       | 1.09 (0.84, 1.41) | 255/230             | 1.18 (0.91, 1.54) |      |
| Low grade                       |                   |                   |                   |                   |                     |      |
| Model 1*                       | 102/228           | 1.00 (ref.)       | 114/235           | 1.07 (0.77, 1.49) | 121/242             | 1.14 (0.82, 1.57) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 1.05 (0.75, 1.46) | 1.13 (0.82, 1.57) | 124/230             | 1.23 (0.89, 1.71) |      |
| Gleason sum 7                  |                   |                   |                   |                   |                     |      |
| Model 1*                       | 70/228            | 1.00 (ref.)       | 62/235            | 0.83 (0.56, 1.23) | 91/242              | 1.17 (0.81, 1.68) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 0.81 (0.55, 1.21) | 1.18 (0.82, 1.70) | 84/230              | 1.09 (0.75, 1.58) |      |
| High grade                     |                   |                   |                   |                   |                     |      |
| Model 1*                       | 25/228            | 1.00 (ref.)       | 16/235            | 0.69 (0.43, 1.09) | 19/242              | 0.80 (0.42, 1.51) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 0.68 (0.43, 1.13) | 0.76 (0.40, 1.45) | 30/230              | 1.36 (0.76, 2.34) |      |
| Lethal*                        |                   |                   |                   |                   |                     |      |
| Model 1*                       | 170/228           | 1.00 (ref.)       | 178/235           | 0.78 (0.50, 1.21) | 209/242             | 1.13 (0.86, 1.14) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 0.98 (0.74, 1.30) | 1.13 (0.86, 1.50) | 217/230             | 1.24 (0.94, 1.63) |      |
| Localised                      |                   |                   |                   |                   |                     |      |
| Model 1*                       | 31/228            | 1.00 (ref.)       | 18/235            | 0.69 (0.47, 1.08) | 28/242              | 1.01 (0.58, 1.75) |      |
| Model 2*                       | 1.00 (ref.)       |                   | 0.71 (0.48, 1.09) | 1.03 (0.59, 1.80) | 26/230              | 1.05 (0.59, 1.89) |      |
| Advanced or lethal*            |                   |                   |                   |                   |                     |      |
| Model 1*                       |                   |                   |                   |                   |                     |      |
| Model 2*                       |                   |                   |                   |                   |                     |      |

Abbreviations: BMI = body mass index; CI = confidence interval; MET = metabolic equivalent; OR = odds ratio; PSA = prostate-specific antigen.

*Adjusted for age at blood collection (continuous, years), age at selection (continuous, years), PSA test before blood collection (yes/no/unknown) and year of blood collection.

**Additionally adjusted for smoking (0, 0.1–20, 20.1–40, 40.1–50 pack-years), BMI (X70, X35 kg m–2), and vigorous physical activity (quartiles, MET-hours per week).

†Gleason sum ≤7.

‡Death by prostate cancer or metastasis in bone or other organs, except lymph nodes.

§Localised or limited extraprostatic extension (T1b, T2b, T3a, and N0M0).

∥Advanced stage (≤T3b, N+; or M+: at diagnosis) or lethal (progression to metastasis or prostate cancer death during follow-up).

Note: Table 2 shows odds ratios (95% confidence intervals) for prostate cancer and subtypes by quartiles of leukocyte telomere length. The data are adjusted for age at blood collection (continuous, years), age at selection (continuous, years), PSA test before blood collection (yes/no/unknown) and year of blood collection. The table includes results for men with and without a family history of prostate cancer, as well as results for subtypes of prostate cancer, including Gleason sum 7 and Gleason sum ≥8.

In this prospective study, we found that longer circulating LTL may be modestly associated with a higher risk of prostate cancer. Longer telomere length was associated with a higher risk of high-grade, advanced stage or lethal disease in men with a family history of prostate cancer. The minor allele of SNP rs7726159 in the TERT gene showed a statistically significant inverse association with prostate cancer, but there was no evidence that this SNP was associated with telomere length in our study.
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Table 3. Odds ratios\(b\) (95% confidence intervals) for total prostate cancer by continuous relative leukocyte telomere length (LTL) within strata of age at blood draw, smoking status and family history of prostate cancer

| Strata                        | Total prostate cancer | High grade\(b\) | Advanced or lethal\(c\) |
|-------------------------------|-----------------------|------------------|------------------------|
|                              | Ca/Co | OR* (95% CI) | P | Ca/Co | OR* (95% CI) | P | Ca/Co | OR* (95% CI) | P |
| Age at blood draw\(d\)        |              |                 |   |              |                 |   |              |                 |   |
| < 64 years                    | 486/492 | 1.17 (1.02–1.34) | 0.02 | 39/492 | 1.26 (0.88–1.79) | 0.20 | 41/492 | 1.05 (0.75–1.47) | 0.79 |
| ≥ 64 years                    | 436/443 | 1.05 (0.92–1.20) | 0.44 | 51/443 | 1.10 (0.82–1.47) | 0.52 | 62/443 | 1.10 (0.84–1.43) | 0.50 |
| Smoking status\(e\)          |              |                 |   |              |                 |   |              |                 |   |
| Never smoker                  | 455/431 | 1.06 (0.92, 1.22) | 0.43 | 39/431 | 1.23 (0.87–1.74) | 0.24 | 43/431 | 0.98 (0.71–1.36) | 0.92 |
| Ever smoker                   | 467/504 | 1.15 (1.01–1.30) | 0.03 | 51/504 | 1.10 (0.82–1.47) | 0.53 | 60/504 | 1.17 (0.89–1.53) | 0.26 |
| No family history of prostate cancer\(f\) | 787/815 | 1.09 (0.98–1.21) | 0.10 | 76/815 | 1.07 (0.84–1.36) | 0.57 | 88/815 | 1.01 (0.81–1.25) | 0.97 |
| Family history of prostate cancer | 135/120 | 1.29 (0.99–1.67) | 0.06 | 14/120 | 2.04 (1.00–4.17) | 0.05 | 15/120 | 2.37 (1.19, 4.72) | 0.01 |

\(\text{Abbreviations: CI = confidence interval; LTL = leukocyte telomere length; OR = odds ratio; PSA = prostate-specific antigen.}\)

\(\text{\(a\)Adjusted for age at blood collection (continuous), years; age at selection (continuous), years; PSA test before blood collection (yes/no/unknown) and year of blood collection.}\)

\(\text{\(b\)Odds ratio.}\)

\(\text{\(c\)Advanced stage (\(p\)T3b, N+, or M+ at diagnosis) or lethal (progression to metastasis or prostate cancer death during follow-up).}\)

\(\text{\(d\)Per s.d. increase in LTL.}\)

\(\text{\(e\)For interaction = 0.85 for total prostate cancer, 0.98 for high-grade and 0.89 for advanced stage or lethal disease.}\)

\(\text{\(f\)For interaction = 0.81 for total prostate cancer, 0.65 for high-grade and 0.48 for advanced stage or lethal disease.}\)

Consistent methodologies are needed. Most of the large epidemiological studies have used qPCR to estimate LTL, since this method enables high-throughput and low amounts of DNA (Cawthon, 2002). The DNA extraction method may also affect telomere length assessment method (FISH assay), including, the telomere length assessment method (FISH assay), the mean or median age at blood draw in all three studies was in the early to the mid-60s. The results from the present study did not show a statistically significant association between longer telomere length and more aggressive prostate cancer (defined as high grade, lethal, advanced stage or lethal); however, we cannot exclude that modest associations exist. We observed a higher risk of more aggressive prostate cancer among men with longer telomeres who also had a family history of prostate cancer. These results are interesting given the finding that paternal age is a determinant of telomere length in offspring (Prescott et al, 2012). However, due to a small sample size and several stratifications, these results should be interpreted with caution.

In summary, our prospective findings suggest that longer circulating LTL may be associated with a higher risk of overall prostate cancer, including more aggressive disease, especially in men who have a family history of prostate cancer.

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