Longer Telomere Length in Peripheral White Blood Cells Is Associated with Risk of Lung Cancer and the rs2736100 (CLPTM1L-TERT) Polymorphism in a Prospective Cohort Study among Women in China

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Abstract

A recent genome-wide association study of lung cancer among never-smoking females in Asia demonstrated that the rs2736100 polymorphism in the TERT-CLPTM1L locus on chromosome 5p15.33 was strongly and significantly associated with risk of adenocarcinoma of the lung. The telomerase gene TERT is a reverse transcriptase that is critical for telomere replication and stabilization by controlling telomere length. We previously found that longer telomere length measured in peripheral white blood cell DNA was associated with increased risk of lung cancer in a prospective cohort study of smoking males in Finland. To follow up on this finding, we carried out a nested case-control study of 215 female lung cancer cases and 215 female controls, 94% of whom were never-smokers, in the prospective Shanghai Women’s Health Study cohort. There was a dose-response relationship between tertiles of telomere length and risk of lung cancer (odds ratio (OR), 95% confidence interval [CI]: 1.0, 1.4 [0.8–2.5], and 2.2 [1.2–4.0], respectively; P trend = 0.003). Further, the association was unchanged by the length of time from blood collection to case diagnosis. In addition, the rs2736100 G allele, which we previously have shown to be associated with risk of lung cancer in this cohort, was significantly associated with longer telomere length in these same study subjects (P trend = 0.030). Our findings suggest that individuals with longer telomere length in peripheral white blood cells may have an increased risk of lung cancer, but require replication in additional prospective cohorts and populations.

Introduction

Telomerase gene TERT is a reverse transcriptase that is critical for telomere replication and stabilization by controlling telomere length. Telomeres are DNA-protein complexes that cap the ends of chromosomes and promote chromosomal stability. To date, the associations between telomere length and cancer risk are inconclusive. Most initial studies used a case-control design and reported that shorter telomere length measured in peripheral white blood cells was associated with increased risk of cancer [1]. In contrast, some recent publications using a prospective cohort design have suggested that longer telomere length may be associated with increased risk of certain tumors, including lung, lymphoma, hepatocellular carcinoma, and melanoma [2–5]. Recently, two case-control studies reported that longer telomere length was associated with colorectal, breast cancer, and breast cancer survival [6–9]. Shorter telomere length has been associated with aging and both shorter and longer telomere length have been associated with risk of a number of chronic diseases [10,11], although this heterogeneity may be explained in part by case-control vs. prospective cohort study designs. In addition, telomere length is strongly mediated by genetic factors with an estimated heritability ranging from 44% to 80% [12,13]. Several studies have identified a number of polymorphisms that were associated with telomere length [8,14–17], but a comprehensive understanding of the genetic contribution to telomere length has still not emerged.

We recently conducted a genome-wide association study (GWAS) of lung cancer among never-smoking females in Asia and demonstrated that the rs2736100 polymorphism in the TERT-CLPTM1L locus on chromosome 5p15.33 was strongly and significantly associated with risk of adenocarcinoma of the...
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Materials and Methods

Study Subjects

The detailed methods for the SWHS have been described previously [27]. Briefly, 74,942 Chinese women between the ages of 40 and 70 years and residing in seven urban communities of Shanghai were recruited into the cohort study from 1997 to 2000 with a participation rate of 92.7%. Of the study participants, 56,831 (75.8%) provided a blood sample, which was collected during enrollment into the cohort. The study was approved by the institutional review boards of all collaborating institutions. Each study subject provided a consent form at the time of enrollment and completed a standardized questionnaire including information on demographic characteristics, medical history, family history of cancer, tobacco use, residential history including use of cooking oil and fuel, and exposure to environmental tobacco smoke from their husband or from colleagues in the workplace. Follow-up for cancer incidence and mortality was conducted through home visits as well as linkage to the population-based Shanghai Cancer Registry. For each study subject, information on cancer, tobacco use, residential history, and family history was obtained by interviewers trained in cancer epidemiology.

We previously reported that longer telomere length was associated with risk of lung cancer in the Alpha-Tocopherol, Beta-Carotenene Cancer Prevention (ATBC) prospective cohort [4], which is comprised of smoking males in Finland. To follow up on this report in a distinctly different population and to further explore our genetic findings, we conducted a nested case-control study of lung cancer cases and controls in the prospective Shanghai Women’s Health Study cohort (SWHS).

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DNA was extracted from buffy coats using the phenol-chloroform method. A monochrome multiplex quantitative PCR assay was used to determine the telomere measurements [28]. All assays were carried out at the laboratory of Dr. Richard Cawthon using the Bio-Rad CFX384 Real-Time PCR Detection System. Masked replicate samples were interspersed within and across assay batches to evaluate assay reproducibility. Cases and controls were assayed consecutively within batches. The overall coefficient of variation (CV) of replicate samples was 11% and intraclass correlation coefficient (ICC) was 87%. In brief, the reagents in the 10 µL PCR were 10 mmol/L Tris-HCl (pH 8.3), 50 mM KCl, 3 mM MgCl2, 0.2 mM each dNTP, 1 mM dNTP, 1 mol/L betaine, 0.75 x SYBR Green I, and AmpliTaq Gold DNA polymerase, 0.625 U. The four primers were (5’ to 3’): telg (at 100 nmol/L), ACAC-

Statistical Analysis

Because the T/S ratios derived from the telomere length data were not normally distributed, the data were log transformed. The Wilcoxon signed-rank test was used to test the difference of telomere length among cases versus controls. The cut points for the tertiles of telomere length were derived from the distribution in the controls. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using conditional logistic regression models. Telomere length was modeled as both a continuous and categorical variable. Tests for trends were calculated using log transformed telomere length as a continuous variable. Age was used in all conditional models and account for potential residual confounding, and smoking status was included in all models that included ever-smokers. Variables that resulted in a 10% or greater change in the β-coefficient of the telomere length variable in the
base model were considered confounders and included in the final, multivariable models. All P values are 2-sided. We also conducted a secondary analysis using fractional polynomials to investigate a possible non-linear association between telomere length and risk of lung cancer. The optimal degree of smoothing was chosen using a model selection procedure proposed by Royston and Sauerbrei [29]. To determine if the association might be driven in part by elevated telomere length among cases with undiagnosed lung cancer at the time of blood sample collection, and to determine if the association persisted for more than 5 years, we stratified the analyses by time from blood collection to case diagnosis (0–2, 2–5, and >5 years) or reference date that the control was selected. We analyzed the influence of the rs2736100 genotype on log-transformed telomere length by linear regression, assigning the ordinal values 1, 2, and 3 for the TT, GT, and GG genotypes, respectively, and adjusting for age.

**Results**

The baseline characteristics of the study subjects are shown in Table 1. The age of cases and controls was comparable and 93% of cases and 95% of controls were never-smokers. Telomere length was inversely correlated with age in both cases (Spearman correlation \( r = -0.39 \) \( P < 0.0001 \)) and controls (Spearman correlation \( r = -0.41 \) \( P < 0.0001 \)). No significant correlation was found between the mean telomere length and demographic parameters shown in Table 1. In addition, the distribution of telomere length

| Characteristic | Controls (N = 215) | Cases (N = 215) |
|---------------|-------------------|----------------|
| N (%)         | N (%)             | N (%)         |
| Age at enrollment, y<sup>2</sup> |                   |                |
| 40–44         | 16 (7.44)         | 15 (6.98)     |
| 45–49         | 23 (10.70)        | 25 (11.63)    |
| 50–54         | 23 (10.70)        | 24 (11.16)    |
| 55–59         | 26 (12.09)        | 26 (12.09)    |
| 60–64         | 44 (20.47)        | 47 (21.86)    |
| 65+           | 83 (38.60)        | 78 (36.28)    |
| Ever Smoking<sup>£</sup> |                   |                |
| Yes           | 10 (4.65)         | 16 (7.44)     |
| No            | 205 (95.35)       | 199 (92.56)   |
| Passive Smoking<sup>£</sup> |                |                |
| Yes           | 161 (74.88)       | 153 (71.16)   |
| No            | 33 (15.35)        | 36 (16.74)    |
| NA<sup>1</sup> | 21 (9.77)         | 26 (12.09)    |
| Family history of lung cancer<sup>£</sup> |                |                |
| Yes           | 1 (0.47)          | 3 (1.40)      |
| No            | 214 (99.53)       | 212 (98.60)   |
| Year of enrollment |                |                |
| 1997          | 61 (28.37)        | 53 (24.65)    |
| 1998          | 97 (45.12)        | 108 (50.23)   |
| 1999          | 47 (21.86)        | 42 (19.53)    |
| 2000          | 10 (4.65)         | 12 (5.58)     |
| Lung cancer histologic subtype |                |                |
| Adenocarcinoma | 93 (43.26)       |                |
| Other/NOS<sup>5</sup> | 122 (56.74) |                |
| rs2736100     |                   |                |
| GG            | 24 (11.16)        | 41 (19.07)    |
| GT            | 103 (47.91)       | 109 (50.70)   |
| TT            | 70 (32.56)        | 43 (20.00)    |
| NA<sup>11</sup> | 18 (8.37)        | 22 (10.23)    |

<sup>1</sup>Spearman correlation (r) with telomere length in controls is \(-0.41\) \((P < 0.0001)\).

<sup>£</sup>P value of spearman r with telomere length in controls >0.05.

<sup>£</sup>Family history of lung cancer in first degree relatives.

<sup>5</sup>NOS indicates not otherwise specified.

<sup>1</sup>NA indicates not available.

<sup>11</sup>NA indicates not available, as only never-smoking subjects were genotyped.

Table 1. Selected characteristic of lung cancer cases and individually matched controls selected from the Shanghai Women’s Health Study (recruited between 1997–2000).
was statistically significantly longer among cases than controls \(P = 0.032\).

The risks of lung cancer by tertiles of telomere length are shown in Table 2. Subjects in the middle and highest tertiles had higher risk than did those in the lowest tertile (OR 1.4, 95% CI 0.8–2.5 for the middle tertile; 2.2, 1.2–4.0 for the highest tertile, \(P\) trend = 0.003, Table 2, adjusted for age and ever smoking). Further adjustment for passive smoking and family history of lung cancer had a negligible impact on the results (OR 1.4, 95% CI 0.8–2.4 and 2.2, 1.2–4.0 for the middle and highest tertiles, respectively, \(P\) trend = 0.004). Removal of ever-smoking cases and controls yielded similar results (OR 1.4, 95% CI 0.9–2.9 and 2.3, 1.3–4.7 for the middle and highest tertiles, respectively, \(P\) trend = 0.003). Models including fractional polynomials did not fit the data better than the simpler linear model (likelihood ratio test \(p = 0.44\)). The latter was thus retained on the ground of parsimony. The observed associations were similar across different follow-up times (Table 2) (i.e., time from date of phlebotomy to date of diagnosis), and a test of heterogeneity for associations across strata of follow-up time was not significant (\(P = 0.15\)). However, due to the small number of subjects in some strata and the imprecise risk estimates, replication in studies with larger samples sizes is needed to evaluate potential heterogeneity. In addition, there was no evidence that the association between telomere length and risk of lung cancer varied by age of blood donation (test for heterogeneity: \(P = 0.96\)).

We previously reported that rs2736100 on chromosome 5p15.33 was strongly associated with risk of adenocarcinoma of the lung among never-smokers in this cohort. We therefore studied the relationship between the genetic data and telomere length in this population. The mean telomere length in association with rs2736100 (\(CLPTM1L\)-\(TERT\)) is shown in Table 3. The rs2736100 G allele, which we previously demonstrated to be associated with risk of lung cancer in this cohort \(19\), was significantly associated with longer telomere length (\(P\) trend = 0.03) (Table 3).

### Discussion

In this prospective cohort study of mostly never-smoking women in China, we found that longer telomere length measured in peripheral white blood cells was significantly and positively associated with increased risk of lung cancer and this association was unchanged by the length of time from blood collection to case diagnosis. Further, the rs2736100 G allele, which we previously demonstrated to be associated with risk of lung cancer in this cohort \(19\), was also significantly associated with longer telomere length.

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**Table 2.** Telomere length and risk of lung cancer: results for overall study and stratifying by years from enrollment to case diagnosis.

| Telomere Length | Overall Age from enrollment to case diagnosis | \(\leq 2\) | >2-5 | >5 |
|-----------------|---------------------------------------------|----------|------|-----|
| \(N_{C}/N_{Ca}\) | OR(95%CI) | \(N_{C}/N_{Ca}\) | OR(95%CI) | \(N_{C}/N_{Ca}\) | OR(95%CI) |
| <1.37 | 71/54 | 1.0 | 12/10 | 1.0 | 26/21 | 1.0 |
| 1.37–1.60 | 72/69 | 1.4(0.8–2.5) | 13/8 | 0.6(0.1–3.0) | 32/26 | 1.3(0.6–3.2) |
| ≥1.60 | 72/92 | 2.2(1.2–4.0) | 12/19 | 4.1(0.7–25.1) | 33/44 | 2.5(0.9–7.1) |
| \(P\) trend | 0.003\(^1\) | 0.16\(^2\) | 0.069\(^2\) | 0.076\(^2\) |

\(^1\)Telomere length categorized using tertiles in controls as cut-points. \(^2\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^3\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^4\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^5\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^6\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^7\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^8\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^9\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^10\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^11\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^12\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^13\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^14\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^15\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^16\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^17\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^18\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^19\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^20\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^21\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking. \(^22\)Odds ratios computed using conditional logistic regression adjusted for age and ever smoking.

**Table 3.** Mean telomere length in association with rs2736100 (\(CLPTM1L\)-\(TERT\)), by case-control status in the Shanghai Women’s Health Study (All cases and controls).

| Genotype | Controls \((\%\) \(\%\)) | Cases \((\%)\) | All \(^3\) | Cases \(^3\) | Controls \(^3\) |
|----------|----------------------|-------------|----------|------------|-------------|
| TT | 70 (36) | 43 (22) | 1.45(0.30) | 1.50(0.34) | 1.43(0.28) |
| GT | 103 (52) | 109 (56) | 1.53(0.29) | 1.56(0.30) | 1.50(0.29) |
| GG | 24 (12) | 41 (21) | 1.55(0.33) | 1.57(0.37) | 1.52(0.25) |
| \(P\) trend \(^4\) | | | 0.030 | 0.20 | 0.20 |
| Correlation \(P\) value \(^5\) | | | 0.035 | 0.20 | 0.20 |

\(^3\)Mean (SD). \(^4\)Log transformed telomere length as continuous variable was used. \(^5\)Correlation \(P\) value from spearman correlation test.

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Our finding that longer telomere length is associated with lung cancer risk is consistent with our previous report in the prospective ATBC Cancer Prevention cohort [4] in male smokers. Both of the two studies are prospective by design and are the only cohort studies of telomere length and lung cancer published to date, to the best of our knowledge. In contrast, some case-control studies have reported associations between shorter telomere length and lung cancer risk [30–32] where telomere length was measured in white blood cells collected at the time of or after diagnosis of cancer. It is interesting that a report from the same cohort found a U-shaped association between telomere length and colorectal cancer risk, suggesting that the relationship between telomere length measured in peripheral blood leukocytes and risk of various types of cancers may exhibit different types of dose-response relationships.

The inconsistency between findings in case-control and cohort studies may be due to a number of reasons. First, telomere length in peripheral white blood cells could be altered by the presence of malignant disease. Therefore, the observed association between shortened telomere length and disease in case-control studies could be a result of reverse causation bias [16,33]. Secondly, chemotherapy or radiation therapy prior to blood collection could cause DNA damage and might affect telomere length [34,35]. Several of the case-control studies of cancer did not report the status of the treatment of the cases. Pooley et al. compared results of telomere length from samples of both retrospective case-control studies and prospective cohort studies of breast and colon cancer patients and found that shorter telomere length was associated with increased risk in the case-control studies but not in the prospective cohort studies [16,33]. Blood samples from subjects in our study were collected one to 10 years prior to diagnosis, and the effects we report persisted for the longest period of follow-up (i.e., more than 5 to 10 years). Third, accuracy and precision in the measurement of telomere length is critical in calculating risk of cancer [36] and variation in these may contribute to inconsistent findings. For example, plate and location of sample on a plate had a significant influence on telomere length measurements even though they are highly correlated between plates within a given individual [36]. The monochrome multiplex quantitative PCR method used in this report, which was developed by Dr. Richard Cawthon [28], provides improved consistency compared to other methods [8]. In our study, Dr. Cawthon's laboratory conducted the analyses with a coefficient of variation (CV) of 11%. Also, we enhanced precision in the measurement of telomere length by putting DNA from cases and their matched controls next to each other on a given plate.

In principle, either long or short telomeres may raise cancer risks, depending on the cell's history of somatic mutations and the cell's microenvironment. When the cell cycle checkpoint, cellular senescence, and apoptosis gene networks are intact, short telomeres in dividing cells are expected to be protective against cancer, since further telomere shortening caused by cell division in additional cohorts and populations.

**Author Contributions**

Conceived and designed the experiments: QL. RC. SC. WZ. NR. Performed the experiments: RC. Analyzed the data: QL. RC. WH. FB. NR. Contributed reagents/materials/analysis tools: RC. Wrote the paper: QL. RC. YG. WH. HDH. FB. BJ. BB. WHC. XS. QC. YX. SB. CK. SC. WZ. NR.

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