A Functional Variant of Tandem Repeats in Human Telomerase Gene Was Associated with Survival of Patients with Early Stages of Non–Small Cell Lung Cancer

Luo Wang¹, Li-E Wang¹, Li Mao², Margaret R. Spitz¹, and Qingyi Wei¹

Abstract

**Purpose:** Elevated levels of human telomerase (hTERT) mRNA in tumors is a marker for poorer survival in patients with stage I non–small cell lung cancer (NSCLC). A functional variant of MNS16A-short tandem repeats in hTERT (S allele) is associated with higher expression levels of hTERT mRNA compared with the MNS16A-long (L) allele. It is unknown, however, whether or not the hTERT MNS16A variant genotype predicts survival of NSCLC patients.

**Experimental Design:** The hTERT genotypes of 808 patients with NSCLC were determined by direct PCR with genomic DNA. Overall median survival times were estimated by the life-table method, and the log-rank test was used to test for homogeneity of the survival curves. Both univariate and multivariate Cox proportional hazards models were used to assess the associations between survival time and the hTERT genotype as well as other known risk factors.

**Results:** The hTERT variant genotype was not associated with overall survival among the 808 patients. However, among 221 patients with stage I or II NSCLC, the S allele was associated with shorter survival time \((P = 0.027\), by log-rank test). The adjusted hazard ratios were 1.30 (95% confidence interval, 0.79-2.14; \(P = 0.310\)) for the SL-genotype and 2.34 (95% confidence interval, 1.20-4.56, \(P = 0.012\)) for the SS-genotype compared with the LL-genotype \((P = 0.021\) for trend test). These findings were not evident in 587 patients with stage III or IV NSCLC.

**Conclusion:** The functional MNS16A-SS genotype may be a marker for poorer survival in early-stage NSCLC.

Lung cancer remains the leading cause of cancer-related death for men and women in the United States (1). Non–small cell lung cancer (NSCLC) accounts for >80% of lung cancers. Although innovative surgical procedures, novel treatment, and effective clinical management have somehow improved the survival (2, 3), few validated biomarkers can predict response to treatment and survival (4). Individual patients vary widely in their response to therapy, which could be attributed in part to genetic differences in the patients.

Recent genome-wide studies of lung cancer have identified a lung cancer susceptibility TERT-CLPTM1L locus on chromosome 5p15.33 (5, 6), particularly for lung adenocarcinoma (7, 8), and this locus has also been reported to predict DNA adduct formation (9). Telomeres, the structures capping the distal ends of chromosomes, function to prevent chromosome degradation, end-to-end fusions, rearrangements, and chromosome loss (10). The genomic instability characteristic of shortened telomeres or telomere dysfunction is associated with senescence and cellular crisis in humans (11). Although the telomere functions to maintain the potential of cellular immortalization, stabilization of telomeres by telomerase more likely leads to immortalization (12). Telomerase is a holoenzyme, and its catalytic subunit (TERT) is the core component responsible for its enzymatic activity. In humans, telomerase activity is undetectable in most normal cells, although peripheral and cord blood (or bone marrow) leukocytes do exhibit telomerase activity (13, 14). However, telomerase reactivation has been reported as one of the most common events in almost all types of human cancers (15).

In a previously published study, we showed that hTERT mRNA levels in tumors were an independent predictor of survival in patients with stage I NSCLC after surgical resection (16). Subsequently, we identified a functional variable number of tandem repeats (VNTR), a variant named MNS16A, in the downstream region of the hTERT gene locus (5p15.33), which has four different alleles that were classified as either short (S) or long (L) alleles on the basis of their functionality (17). Further experiments...
Translational Relevance

This study provides some evidence that the human telomerase (hTERT) MNS16A variant genotype may be a marker for survival of stage I and II non–small cell lung cancer (NSCLC) patients. This finding is consistent with previous reports that elevated levels of hTERT mRNA in tumors is an independent marker for poorer survival in patients with stage I NSCLC and that this MNS16A-short tandem repeats in hTERT (S allele) is associated with higher in vitro expression levels of hTERT mRNA compared with the MNS16A-long (L) allele. This finding has some clinical implication, given that TERT has been identified in genome-wide association studies of lung cancer as a susceptibility locus, particularly for lung adenocarcinoma.

shown that the MNS16A VNTR was associated with initiation of an antisense RNA transcript (unpublished data) whose function remains uncertain. However, the MNS16A-S allele was associated with higher levels of the MNS16A-antisense RNA transcripts, compared with the MNS16A-L allele, and the level of this antisense RNA transcript parallels that of hTERT mRNA in all telomerase-positive NSCLC cell lines and primary lung cancer tissues (16). Based on these observations, we hypothesized that the MNS16A-S allele, compared with the L allele, is associated with poorer survival in NSCLC patients. In this study, we evaluated the association between the hTERT genotype (based on the S and L alleles defined by MNS16A VNTR) and survival in NSCLC patients with different tumor-node-metastasis (TNM) staging tumors.

Materials and Methods

Study population

Patients were recruited for an ongoing hospital-based case-control epidemiologic study of lung cancer from The University of Texas M. D. Anderson Cancer Center, Houston, Texas, during the period from July 1995 to September 2003 (18). A total of 1,056 patients newly diagnosed with histopathologically confirmed NSCLC were available for analysis. There were no age, stage, or histology restrictions, but all patients were untreated. Blood samples were obtained from each subject after written informed consent and completion of a standardized personal interview before the therapy was instituted. The research protocol was approved by the institutional review board of M.D. Anderson Cancer Center.

Patient clinical follow-up information was obtained from chart review and from the M. D. Anderson institutional database. Only non-Hispanic white patients who were residents of Texas at the time of diagnosis were included because there were too few patients of other ethnicities for meaningful statistical analysis. As a result, a total of 808 NSCLC patients were included for this survival analysis. Patients were followed from the date of diagnosis to the date of last follow-up or date of death through September 2004. The patients were followed up to 10 years for the longest. Survival in months was calculated as the time between the diagnosis date and the last contact date (or date of death).

DNA extraction and genotyping of MNS16A

For each blood sample, a leukocyte cell pellet was obtained from the buffy-coat layer by centrifugation of 1 mL of whole blood. The genomic DNA was extracted by using the Qiagen DNA blood mini kit (Qiagen) according to the manufacturer’s instruction. DNA purity was evaluated by electrophoresis on a 1% agarose gel and the concentration was determined by UV spectrophotometry.

We genotyped the MNS16A VNTR by PCR using the primer set as previously reported (16). The sequence of forward primer was 5′-AGGATTCTGATCTCTGAAAGGGTG-3′, and the reverse primer 5′-TTCGCCCTGAGGAAGACGTATG-3′. A PCR reaction mixture (10 μL) was assembled with 40-ng genomic DNA, 2.5 pmol of each primer, 1× PCR buffer (50 mmol/L KCl, 10 mmol/L Tris-HCl, pH 8.3), 1.5 mmol/L MgCl2, 0.1 mmol/L each dNTP, and 1 U Taq polymerase (Sigma-Aldrich Biotechnology). The PCR reaction was done with a PTC-200 DNA Engine (Peltier Thermal Cycler, MJ Research Inc.). The amplification procedure consisted of an initial denaturing step with 5 minutes at 95°C, followed by 35 cycles of 30 seconds at 95°C, 45 seconds at 60°C, and 1 minute at 72°C, as well as a final extension step with 10 minutes at 72°C. All PCR products were visualized on a 2% agarose gel containing 0.25 μg/mL of ethidium bromide.

Among the cases genotyped for the MNS16A, four samples (0.4%) were excluded because the genotyping results were not consistent on repeated assay. About 14% of the samples were randomly repeated with 100% concordance of results.

Statistical analysis

We grouped the patients by age at diagnosis (<45, 45-59, and ≥60 years old), common histologic type (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma), and clinical stage (TNM stage I or II, stage IIIa or IIIb, and stage IV). Subjects who had smoked >100 cigarettes in their lifetime were defined as “ever smokers” and they were further divided into “former smokers,” who had quit smoking at least 1 year prior to diagnosis, and the rest were “current smokers”. The χ2-test was done to test for the difference in the distributions of hTERT genotypes defined by the MNS16A alleles as well as the demographic variables and clinicopathologic features. Overall median survival times were estimated by the Kaplan-Meier method and the log-rank test was used to test for homogeneity of the survival curves. Both univariate and multivariate Cox proportional hazards models were used to assess the association between survival time and risk factors, including age at diagnosis, sex, pack-years smoked, histopathologic types, treatment,
and the hTERT MNS16A/VNTR genotype. The hazard ratio (HR) was calculated with adjustment for these covariates in the same model. All P values were determined by two-sided tests. All statistical analysis was carried out with Statistical Analysis System software (Version 8e; SAS Institute Inc.).

Results

In the 808 eligible NSCLC patients, there were 432 (53.5%) males and 376 (46.5%) females with ages ranging between 33 and 85 years (mean diagnosis age 61.5 ± 10.0 for males and 60.3 ± 10.2 for females). All patients were self-reported non-Hispanic whites. There were 139 (17.2%) never smokers and 669 (82.8%) ever smokers including 348 (43.1%) former smokers and 321 (39.7%) current smokers. The majority of patients were diagnosed with adenocarcinoma (57.4%), and the remaining diagnoses were 204 (25.2%) squamous cell carcinoma, 32 (4.0%) large cell carcinoma, and 108 (13.4%) unclassified NSCLC tumors. Overall, these 808 NSCLC patients consisted of 27.3% (n = 221) clinical stage I (n = 156) or II (n = 65), 39.0% (n = 315) stage III, and 33.7% (n = 272) stage IV.

Genotyping results of the MNS16A VNTR showed seven (A to G) distinct patterns in this study population (Fig. 1A) with a frequency distribution of 2.0% for A, 42.1% for B, 1.7% for C, 0.7% for D, 42.6% for E, 1.5% for F, and 9.4% for G based on the combinations of the four alleles named as MNS16A VNTR-243, VNTR-272, VNTR-302, and VNTR-333 (17). Figure 1B shows the schematic sequence difference of these four alleles. These alleles consist of two basic elements (i.e., A and B) with or without an “AATC” insertion, and we classified the allele VNTR-243 and VNTR-272 as the S-allele, and VNTR-302 and VNTR-333 as the L-allele on the basis of their functional relevance (17). Therefore, the hTERT genotypes of the MNS16A VNTR were defined as either SS, SL, or LL genotype.

Although there were no overall statistically significant differences in distribution of the hTERT MNS16A genotypes by age, sex, smoking status, tumor histology, or clinical stage of 808 patients with NSCLC (data not shown), the SS genotype was present in 5.8% of never smokers, 11.1% of former smokers, and 12.8% of current smokers (P = 0.038 for trend test). The overall survival of the 808 NSCLC patients grouped by histopathologic type or stage is graphed in Fig. 2A and B. As expected, tumor stage remains the best predictor for overall survival of NSCLC patients. The median survival times were 64.9 months for stage I or II NSCLC, 18.9 for stage III, and 11.6 for stage IV (P < 0.001, by log-rank test). There were no survival differences by the hTERT MNS16A genotype overall (Fig. 2C).

Because we previously found an association between tumor hTERT mRNA expression and poorer survival in stage I NSCLC patients (16), we focused on the 221 stage I or II patients who were grouped by surgery alone, or in combination with radiation or chemotherapy. The majority of these stage I or II patients (132 cases) were diagnosed with adenocarcinoma and the remaining (nonadenocarcinoma) were squamous cell carcinoma (75 cases), large cell carcinoma (6 cases), and unclassified (8 cases). There was no association by genotypes in 587 stage III and IV patients (Fig. 2D). However, the median survival time in patients with the hTERT MNS16A-S variant (SL and SS) genotypes was statistically shorter (P = 0.027 by log-rank test) than that in patients with the hTERT MNS16A-LL genotype in these 221 stage I or II NSCLC patients (Fig. 3). Among these 221 cases, there were 143 (64.7%) patients still alive and 78 dead (35.3%) at the last follow-up. The median survival rates for these patients were significantly different by hTERT MNS16A-genotypes at 36.8 months for the SS-genotype, 64.9 months for the SL-genotype, and 70.0 for the LL-genotype (Fig. 3).
We then used the univariate and multivariate Cox proportional hazard models to evaluate HRs associated with the hTERT MNS16A genotypes with adjustment for age at diagnosis, sex, smoking status, tumor histology, and treatment. Among all known variables shown in Table 1, the only significant predictor was nonadenocarcinoma compared with adenocarcinoma ($P = 0.044$). However, compared with the LL genotype, the hTERT MNS16A-S variant genotypes were also associated with increased HRs in an allele-dose response manner (HR, 1.30; 95% confidence interval, 0.79-2.14 for the SL genotype; HR, 2.34; 95% confidence interval, 1.20-4.56 for the SS genotype). The trend test for increased HRs with the increasing numbers of S-allele was statistically significant ($P = 0.021$).

**Discussion**

In the present survival analysis, we showed that the hTERT MNS16A SS genotype was associated with a significantly shorter survival time in early-stage (I or II) NSCLC patients, compared with the LL genotype as assessed in the multivariate Cox hazard model. In a previous study, we had shown that the hTERT MNS16A-S allele was correlated with elevated hTERT mRNA expression levels compared with the L allele and that the elevated hTERT mRNA...
expression levels in tumors were associated with poorer survival in patients with stage I NSCLC (17). Therefore, our present findings are consistent with the previously observed association between increased hTERT expression in tumors and poorer survival in stage I NSCLC patients but not evident in patients with advanced diseases (16). It is known that hTERT mRNA overexpression is correlated with reactivated telomerase in the lungs of cigarette smokers (19) and that the shorter telomeres are associated with increased risks for human cancers (20). However, our results provide a possible genetic mechanism for the previously observed association between increased hTERT expression in tumors and poorer survival in stage I NSCLC patients (16). Our findings are biologically plausible, because both telomere and telomerase activity have implications in tumorigenesis.

The hTERT gene is located on chromosome 5p15.33 and has 16 exons (21, 22) that can be further divided into four exon-clusters according to the distribution of many minisatellites and microsatellites (16). All seven reported major conserved motifs of the telomerase subunit (23) are located in the second cluster (T, 1, 2, and A motifs) and third cluster (B, C, D, and E motifs). Except for a 430-bp EcoRV–BamHI fragment from the hTERT B–E motif, we found that a clear antisense RNA expression signal was always accompanied with hTERT mRNA expression signal detected by in situ hybridization with single-strand specific riboprobes made from several regions of hTERT cDNA (unpublished data).

Further exploration of this phenomenon eventually led to identification of the first antisense RNA transcript in the hTERT gene locus (unpublished data). To date, approximately 85% of all cancer tissues tested are reported to be telomerase positive (12). Similarly, hTERT expression is also detectable in approximately 85% of NSCLC tissues, and the remaining small telomerase-negative minority maintain their telomeres by an alternative lengthening of telomeres mechanism (24). Studies have shown that after surgical treatment, the levels of hTERT mRNA levels in serum were significantly reduced (25), further suggesting the origin of hTERT mRNA levels was in tumors (26).

Table 1. Univariate and multivariate analysis of 221 stage I or II NSCLC patients with Cox proportional hazard model for the death relative risk associated with clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>HR (95% CI)</th>
<th>P*</th>
<th>Adjusted HR (95% CI)†</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>9</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>45-59</td>
<td>57</td>
<td>1.13 (0.26-4.96)</td>
<td>0.87</td>
<td>0.88 (0.20-3.93)</td>
<td>0.87</td>
</tr>
<tr>
<td>≥60</td>
<td>155</td>
<td>2.10 (0.51-8.61)</td>
<td>0.3</td>
<td>1.48 (0.35-6.27)</td>
<td>0.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>102</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>119</td>
<td>0.63 (0.40-0.99)</td>
<td>0.04</td>
<td>0.76 (0.48-1.20)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>20</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>118</td>
<td>1.13 (0.48-2.67)</td>
<td>0.79</td>
<td>0.83 (0.35-2.01)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoker</td>
<td>83</td>
<td>1.47 (0.62-3.52)</td>
<td>0.39</td>
<td>1.12 (0.46-2.72)</td>
<td>0.81</td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>132</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonadenocarcinoma</td>
<td>89</td>
<td>1.89 (1.21-2.96)</td>
<td>0.01</td>
<td>1.61 (1.01-2.57)</td>
<td>0.04</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + radiation</td>
<td>18</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>203</td>
<td>0.88 (0.40-1.91)</td>
<td>0.74</td>
<td>0.77 (0.35-1.69)</td>
<td>0.52</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>27</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>194</td>
<td>1.01 (0.49-2.12)</td>
<td>0.97</td>
<td>1.01 (0.48-2.11)</td>
<td>0.98</td>
</tr>
<tr>
<td>Surgery + combination‡</td>
<td>37</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>184</td>
<td>0.86 (0.47-1.56)</td>
<td>0.61</td>
<td>0.82 (0.45-1.50)</td>
<td>0.52</td>
</tr>
<tr>
<td>hTERT MNS16A-genotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LL-genotype</td>
<td>96</td>
<td>Ref.</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL-genotype</td>
<td>99</td>
<td>1.12 (0.69-1.83)</td>
<td>0.65</td>
<td>1.30 (0.79-2.14)</td>
<td>0.31</td>
</tr>
<tr>
<td>SS-genotype</td>
<td>26</td>
<td>2.35 (1.22-4.53)</td>
<td>0.01</td>
<td>2.34 (1.20-4.56)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviation: 95% CI, 95% confidence interval.
*Two-sided χ²-test.
†Adjusted for sex, smoking status, histology and treatment, where appropriate.
‡Combination of radiation and chemotherapy.

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Because higher expression levels of MNS16A-antisense RNA transcript were found to be associated with the MNS16A-S allele (16), we tested the hypothesis in this study that the MNS16A-S allele is associated with poorer prognosis in NSCLC patients, especially in early-stage disease. Indeed, we found significantly shorter median survival time for the 221 patients with stage I or II NSCLC, who were carriers of the hTERT MNS16A SS variant genotype, whereas we did not observe any effect of the hTERT MNS16A/VNTR genotypes on survival in patients with stage III and IV NSCLC. However, these data need to be replicated by larger studies.

In general, the length of telomeres and telomerase activity do not have the same implications in cancer etiology. One of the underlying mechanisms for age-related cancer risk is an age-related telomere shortening that limits the replicative lifespan of primary human cells, which might play a role in both aging and cancer etiology (27). Telomeres may also indirectly affect DNA repair mediated by the binding of Ku80, a critical protein for nonhomologous DNA double-strand break repair and site-specific recombination of V(D)J gene segments (28). Such interference with repair activity may increase genetic instability due to unrepaired DNA damage, suggesting that telomere dysfunction may be one of the most important molecular mechanisms responsible for genetic instability and thus may play an important role during tumorigenesis (29, 30). Short telomeres were found to be associated with increased risks for human bladder, head and neck, lung, and renal cell cancers in an epidemiologic case-control studies (20). Interestingly, it is reported that there is a significant correlation between telomere length and hTERT mRNA expression level in cancer tissues and adjacent mucosa samples and that telomeres were significantly shorter in colorectal carcinoma tissue than that in adjacent mucosa (10).

Telomerase is inactive in almost all normal somatic epithelial cells in humans, and telomerase activation leads to cell immortalization and tumorigenesis (15, 31, 32). We have previously reported that hTERT mRNA expression was detectable in about 64% of bronchial biopsy specimens (170 of 266) obtained from chronic smokers without lung cancer, suggesting that hTERT reactivation could be a smoking-induced event, one of the precursors in tumorigenesis (19), although the exact underlying mechanism needs to be further explored.

In summary, on the basis of our early observations that (a) hTERT mRNA expression was an independent prognostic marker for stage I NSCLC patients after surgery resection treatment; (b) an antisense RNA transcript expression level was well correlated with hTERT mRNA expression level; (c) a genetic variant VNTR MNS16A was responsible for initiation of this antisense RNA transcript; and (d) the MNS16A-S allele was associated with higher expression level of MNS16A-antisense RNA transcript, we further evaluated the prognostic value of the hTERT genotypes defined by MNS16A/VNTR in the TNM staging subgroups of NSCLC patients. We concluded that the hTERT MNS16A-SS genotype was associated with poorer prognosis in early-stage NSCLC patients, and therefore the hTERT genetic variation, i.e., the hTERT MNS16A genotype, may serve as a potential prognostic biomarker of early-stage NSCLC. Future large studies with clinically homogenous subsets of patients, which would allow further stratification analysis, such as by adenocarcinoma and nonadenocarcinoma, are needed to confirm our findings. The functional relevance of the MNS16A/VNTR as well as the therapeutic potential in pharmacogenomic studies by targeting hTERT also warrants further investigations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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