Systematic review of genetic variation in chromosome 5p15.33 and telomere length as predictive and prognostic biomarkers for lung cancer

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Abstract

Lung cancer remains the leading cause of cancer mortality worldwide. Known histomolecular characteristics and genomic profiles provide limited insight into factors influencing patient outcomes. Telomere length (TL) is important for genomic integrity, and has been a growing area of interest as agents targeting telomerase are being evaluated. Chromosome 5p15.33, an established cancer susceptibility locus, contains a telomerase regulatory gene, TERT, and CLPTM1L, a gene associated with cisplatin-induced apoptosis. This review offers a summary of the clinical utility of 5p15.33 polymorphisms and TL. A total of 621 abstracts were screened and 14 studies (7 for 5p15.33, 7 for TL) were reviewed. Endpoints included overall survival (OS), progression-free survival (PFS), therapy response and toxicity. Of the 23 genetic variants identified, significant associations with OS and/or PFS were reported for rs401681 (CLPTM1L), rs4975616 (TERT-CLPTM1L), and rs2736109 (TERT). Both shorter and longer TL, in tumor and blood, was linked to OS and PFS. Overall, consistent evidence across multiple studies of 5p15.33 polymorphisms and TL was lacking. Despite the potential to become useful prognostic biomarkers in lung cancer, the limited number of reports and their methodological limitations highlight the need for larger, carefully designed studies with clinically defined subpopulations and higher resolution genetic analyses.
Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide (1). Despite recent advances in its treatment, the general prognosis for lung cancer remains poor, with low 5-year survival rates of under 15% (2). For non-small cell lung cancer (NSCLC), treatment with platinum-based chemotherapy provides modest improvements in the survival of stage IIIIB/IV NSCLC patients and the absolute cure rates in Stage II/IIIA. However, our current understanding of the factors influencing inter-individual variability in outcomes is limited, as clinic-demographic factors (age, sex, smoking, disease stage) and histomolecular factors, including tumor histology, somatic molecular changes, such as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements only provide a partial picture (3). This underscores the need to identify non-invasive, reliable molecular markers of disease progression and treatment efficacy.

Telomeres are structures that cap the ends of linear chromosomes and are composed of short tandem repeats of the TTAGGG sequence (4, 5). Telomeres shorten by 20 to 200 base pairs with each round of cell division, due to incomplete DNA replication (6, 7). This occurs in all normal human cells with the exception of adult stem cells and activated lymphocytes (8, 9). Once telomeres become critically short, activation of cell cycle arrest leads to replicative senescence, followed by apoptosis (10). This mechanism represents a fundamental barrier to cancer initiation by limiting proliferation and maintaining genome stability. Therefore, maintenance of telomere length (TL) is a key step in tumorigenesis, and a universal characteristic of immortalized cancer cells (10, 11). The most important telomere lengthening mechanism requires telomerase, an enzyme that is overexpressed in ~90% of tumors, but inactive in normal cells (12). Telomerase-independent, alternative lengthening of telomeres (ALT) pathways are also relevant, but only occur in a small subset of lung carcinomas originating from neuroendocrine cells (10, 11, 13).

One of the genes critical for maintaining the functionality of telomerase is TERT, which is located in chromosome 5p15.33 and encodes the catalytic subunit of telomerase. 5p15.33 (TERT) is one of several genetic loci involved in TL regulation, along with 3q26 (TERC), 4q32.2 (NAF1), 10q24.33 (OBFC1), and 20q13.3 (RTEL1) (14-16). Importantly, genome-wide association studies (GWAS) have established 5p15.33 as an important cancer susceptibility locus (17, 18), but few studies have explored the prognostic (i.e.: overall, progression, or disease-free survival) or predictive (i.e.: treatment response) value of these risk variants.

Functional studies have also suggested that TERT may act as a direct transcriptional regulator of key oncogenic signaling pathways, affecting the induction of target genes critical for cell survival and cancer progression, such as Wnt, Myc NF-κB and β-catenin (19-21). Activation
of EGFR signaling has also been suggested as a mechanism through which TERT stimulates proliferation (11, 22). In addition to TERT, the 5p15.33 region contains another cancer susceptibility gene: CLPTM1L, which encodes the cleft lip and palate-associated transmembrane 1 like protein, and was shown to have a role in cisplatin-induced apoptosis (23).

Another compelling observation is the inhibition of telomerase and telomere shortening in response to platinum-based and radiation therapy, suggesting that TL and TERT may modulate treatment efficacy (24-27). In addition to genetic variation and treatment, TL may also be affected by lifestyle and environmental factors, such as cigarette smoking, alcohol consumption, and air pollution, as well as socioeconomic factors and psychological stress (28-34). These findings demonstrate that TL is a complex and integrative biomarker that captures the influence of a wide range of potentially relevant factors.

The motivation for the present review is to provide a comprehensive discussion of the relationship between TL, inherited genetic variation in 5p15.33 and the clinical outcomes in lung cancer. The prognostic value of TL in solid tumors was previously reviewed by Bisoffi et al. (35) and Svenson et al. (36); however, both articles did not focus on lung cancer. A recent meta-analysis of TL and cancer prognosis by Zhang et al (37) did not provide a summary estimate for lung cancer, and only included two studies. As the evidence for the clinical utility of TL and genetic variants within the TERT/CLPTM1L locus continues to accumulate, we conducted a systematic review of both TL and 5p15.33 genetic variants to integrate current knowledge related to lung cancer prognosis.

Materials and Methods

Search strategy and eligibility criteria

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (38) methodological guidelines were followed, while incorporating a modified protocol for systematic review of the association between chronic stress and telomere length (39) (PROSPERO registration number: CRD42014009274). Telomerase activity is not a surrogate for TL in a blood or tissue sample, which is a culmination of multiple processes affecting telomere homeostasis, such as replication rate, regulatory proteins, telomerase expression, as well as inherited genetic variation and environmental exposures. For this reason, we limited our review to the prognostic effects of TL, and excluded the evaluation of telomerase activity.

A detailed search strategy was developed (Supplementary Methods and Materials), using specific medical subject headings (MeSH) and words from ‘all fields’ to identify studies in MEDLINE (PubMed interface), including the following keywords: “5p15”, “TERT”, “CLPTM1L”,...
“telomere length”, “polymorphism”, “single nucleotide polymorphism”, “genetic variant”, “lung cancer”, “outcome”, “survival”, “prognosis”, “response”, “chemotherapy”, and “radiotherapy”. Searches were also performed using EMBASE (OVID interface; 1947–January 2016) and Google Scholar. Literature searches were carried out independently by two reviewers (LK and LL), and were limited to human studies and English language. Only full reports published on or before January 10, 2016 were included. To ensure sensitivity of the search strategy, citation lists of retrieved articles were checked.

Abstracts of articles that considered any of the following major outcomes were reviewed: overall survival rate, median survival time, disease-free survival rate, progression-free survival, cancer-specific survival, time to progression, and therapy response, including toxicity. Search results were reviewed to exclude studies of cancer risk (incidence) and descriptive reports detailing the correlation between TL and clinic-pathologic characteristics.

Inter-rater agreement in abstract screening was assessed using Cohen’s Kappa, and the two reviewers showed a high level of agreement (0.83, 0.66-0.99) for the identification of eligible studies. Discrepancies in eligibility were resolved through discussion between the two reviewers. The final list of eligible studies was confirmed by a senior epidemiologist (RH).

Data extraction

Screening of full-text manuscripts and data abstraction were completed independently by two reviewers (LK and LL) using a standardized data collection form, a modified version of the template by Quinlan et al. (39), with explicit inclusion and exclusion criteria (Supplementary Methods and Materials). This approach was adopted to ensure homogeneity of data collection and to minimize subjectivity in the data gathering and entry process. The following data were extracted from eligible studies: authors’ names; year of publication; number of case subjects and events; ethnicity; cancer type and histology; statistical analysis methods; summary effect estimates, such as odds ratios (OR), hazard ratios (HR), and their corresponding 95% confidence intervals (CI); estimates of survival time, such as 5-year survival rates or median survival. Covariate data such as inclusion/exclusion criteria of lung cancer patients in each study, and stratification or adjustment variables used in the study analyses were recorded.

For studies of 5p15.33 variants, the names and genomic position of each SNP, the minor allele and genetic model tested were also collected. For studies of TL, we collected information on the DNA source and method of extraction, as well as the method of TL measurement and analysis. Complete concordance (100%) was reached for all variables assessed.
Given the variable outcomes of interest, differences in methodology for TL assessment, and diverse clinical populations, a meta-analysis was not pursued.

**Scientific quality assessment**

Study quality for observational studies was assessed using the Strengthening the Reporting of Genetic Association Studies (STREGA)(40) and Strengthening the Reporting of Observational Studies in Epidemiology: Molecular Epidemiology (STROBE-ME)(41) tools. Experimental designs were assessed using the Consolidated Standards of Reporting Trials (CONSORT) checklist (42). The purpose of this assessment was to identify studies that should be considered for exclusion on the basis of low quality, or failing to report key information. All studies were found to be of acceptable quality and none were excluded using these criteria.

**Results**

A total of 620 relevant titles and abstracts (385 for TL; 235 for 5p15.33) were identified and screened, and 26 (9 for TL; 15 for 5p15.33) were selected for detailed full-text review (Supplementary Figure 1). Relatively few publications were selected for full review because the majority of the articles were focused on functional characterizations of the 5p15.33 locus, TERT/CLPTM1L expression, or telomerase activity. Among epidemiologic studies, only articles relevant for lung cancer prognosis were included. Among the 15 articles selected for full text review, 8 GWAS of lung cancer survival were excluded because they did not report associations for the 5p15.33 region, either in the main text or in the Supplementary Methods and Materials. After these exclusions, 7 studies of genetic variants in 5p15.33 (Supplementary Table S1) were included. After reviewing 9 studies of TL, one report was excluded because it only presented descriptive analyses of TL alterations in lung tumors (43), and another study had an English abstract, but the full text was only available in Japanese (44). A total of 7 studies of TL (Supplementary Table S2) were included in this review.

A range of outcomes was investigated across the 7 studies of 5p15.33 and 7 studies of TL: All-cause mortality was the most common, with overall survival (OS) as the primary outcome, followed by progression-free or disease-free survival (PFS) or risk of disease recurrence, and therapy response. Studies of OS reported median follow-up times of less than 5 years, and relied on electronic healthcare and cancer registry records, as well as active follow-up, to improve the completeness of outcome ascertainment. Censoring was typically defined as the date of the last physician visit. All of the studies were relatively comparable in terms of the statistical analysis methods used. Cox proportional hazards regression were used in studies of OS and PFS, while logistic regression was used in the three studies investigating therapy response. Of the studies...
examining OS, only one study treated deaths from non-lung cancer causes as competing events and estimated sub-hazard ratios (SHR) using the Fine & Gray method (45).

Survival rates and median survival times or time to disease progression or recurrence was estimated using the Kaplan-Meier method. Only one study compared Kaplan-Meier curves using the log rank test as the only method of testing associations with OS and PFS (46). Of the 10 studies that used Cox regression, only two (47, 48) reported verifying the important proportionality assumption.

Chromosome 5p15.33 genetic variants: study description and methods

A total of 23 genetic variants were investigated in the seven studies of 5p15.33 (Supplementary Table S1). Of these, four (57%) were conducted in NSCLC patients (46, 49-51), one study focused on small cell lung cancer (SCLC) (52), and two studies included multiple histological types (47, 53). Xun et al. (47) investigated a mixed case-series of NSCLC (including large cell), SCLC, and unspecified histology, but presented results stratified by histological subtype. Liang et al. (53) evaluated 309 patients: 37.5% squamous carcinoma, 35.6% adenocarcinoma, 21.3% small cell, 0.6% large cell, and 5% unspecified histology. Of these, 115 cases contributed to the therapy response analysis, but the histology distribution of this subset was not specified.

Among the four NSCLC-specific studies, Azad et al. (50), de Mello et al. (46), and Zhao et al. (51) focused exclusively on Stage III/IV disease, while a case series by Catarino et al., was comprised of 89% Stage III/IV patients (49, 51). Azad et al. (50) included an ethnically mixed (74% Caucasian) sample, and the remaining two studies were in European populations. In addition, Azad et al. also restricted analyses to Caucasian patients to minimize confounding by population stratification and verify the consistency of the observed associations (50). All NSCLC studies included several histological subtypes. The cases in Azad et al. (50) and Zhao et al. (51) were similar in their respective histology distributions: adenocarcinoma (61% and 63%, respectively), squamous (24% and 22%) and other NSCLC (15% and 13%). Similarly, adenocarcinoma was most common histology (48.3%) in Catarino et al. (49), followed by squamous carcinoma (37.5%) and other NSCLC (14.2%). The patients investigated by de Mello et al. (46) were divided into squamous (22.9%) and non-squamous (77.1%) groups. Studies with multiple histologies were conducted in European (46, 47, 49) and Han Chinese populations (53). The single SCLC study was conducted in Han Chinese patients (52).

Chromosome 5p15.33 genetic variants: overall survival
Of the seven studies investigating the TERT and CLPTM1L polymorphisms in 5p15.33, five (71%) reported associations for OS (Table 1). However, only two variants in CLPTM1L, rs401681 and rs402710, were examined in multiple studies for this outcome.

Inconsistent results were observed across studies for rs401681. The two NSCLC studies found either no association with OS (50) or a longer median survival among 144 Portuguese NSCLC patients in patients carrying the T allele (46). In contrast, in 874 Han Chinese SCLC patients, carriers of the T allele had a higher risk of death compared to those with the CC genotype (HR=1.29, 95% CI=1.08–1.55) (52). Statistically significant associations were observed in males (HR=1.15, 95% CI=1.01–1.31) and smokers (HR=1.17, 95% CI=1.02–1.34) (52). Differences in tumor subtype and ethnic groups might account for differences in results. Of concern, the positive findings of de Mello et al. (46) were based on unadjusted comparisons of Kaplan-Meier survival curves, and therefore do not account for known differences in prognostic factors.

No statistically significant OS associations were observed for rs402710-T in North American (50) and European (46) NSCLC populations. Although the overall OS association was also absent, in stratified analyses of data from the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort, Xun et al. showed that rs402710-T was associated with lung cancer-specific mortality in current smokers (SHR=1.21, 95%: 1.02–1.43), SCLC patients (SHR=1.57, 95% CI=1.09–2.25), and patients with unspecified lung cancer histology (HR=1.31, 95% CI=1.02–1.68) (47).

Three studies investigated additional genetic variants in this chromosomal region. Firstly, the Canadian study by Azad et al. investigated 8 genetic variants in 5p15.33 that were previously associated with lung cancer risk (50). In their predominantly Caucasian sample of 564 Stage III/IV NSCLC patients, only rs4975616-A (TERT-CLPTM1L) was statistically significantly associated with OS (per allele HR=0.75, 95% CI=0.69–0.91), after adjusting for multiple comparisons and relevant covariates (50). Secondly, Catarino et al. (49) investigated one TERT polymorphism (rs2735940) in 226 Portuguese NSCLC patients, and observed a statistically significant improvement in OS in carriers of the T allele (HR=0.52, 95% CI=0.35–0.77). In analyses stratified by histology, this association remained statistically significant only among patients with non-squamous (adenocarcinoma and other) tumors (HR=0.46, 95% CI=0.27–0.78) (49). Thirdly, De Mello et al. reported a significant (unadjusted) association with OS for rs31489 (46). For patients with non-squamous NSCLC, the rs31489 AA and CA genotypes had longer survival than the rs31489 CC genotype: 13 months (range: 6.98–19.01), and 13 months (range: 6.33–19.66),
compared to 6 months (range: 1.10–10.90), respectively (p=0.029) (46). None of these polymorphisms were evaluated in more than one study.

**Chromosome 5p15.33 genetic variants: disease progression**

Three studies investigated 5p15.33 polymorphisms with respect to PFS in Stage III/IV patients (Table 2). There was some variation in the assessment of PFS among these studies. Specifically, the relevant time period started at diagnosis in the study by Azad et al. (50), while Zhao et al. (51) considered time only after the start of chemotherapy. This also reflects differences in the eligibility criteria, since Zhao et al. (51) only included patients who have undergone chemotherapy.

Both studies found rs401681 to be significantly associated with PFS. Azad et al. reported a decreased likelihood of cancer progression for carriers of the T allele (HR=0.86, 95% CI=0.76–0.99), and de Mello et al. observed significantly improved PFS (log-rank p=0.021) in patients with the rs401681-TT genotype (7 months, range: 0.001–14.04), compared to CC (2 months, range: 0.95–3.05) and CT (5 months, range: 3.22–6.77) genotypes (46) (50). In addition, Azad et al. observed a significant association with PFS for rs4975616-A (HR=0.74, 95% CI=0.62–0.89)(50).

A third study by Zhao et al. (51) reported inconsistent results for rs2736109, where longer progression-free time was observed for GA genotypes (p=0.023) compared to GG, but increased progression likelihood was observed for rs2736109-AA (HR=1.32, 1.03–1.68). This pattern was more pronounced for individuals aged >58 (log-rank p=0.007; HR=0.65, 95%CI=0.50–0.85) (51).

**Chromosome 5p15.33 genetic variants: treatment response**

Three studies investigated response to chemotherapy. Although treatment response was assessed using the Response Evaluate Criteria in Solid Tumor (RECIST) guidelines (54), all studies operationalized their outcome variables differently (Table 3). Liang et al. (53) investigated 9 variants in 5p15.33, of which two CLPTM1L SNPs (rs401681-T, rs402710-T) were also investigated by De Mello et al. (46). However, the two populations were very different, and were thus treated differently, albeit both using platinum-based multi-agent chemotherapeutic regimens. De Mello et al. evaluated Portuguese Stage III/IV NSCLC patients, including a subset positive for EGFR mutations treated with gefitinib, whereas Liang et al. examined extensive stage SCLC patients of Han Chinese descent. Neither study observed statistically significant associations with treatment response.

Zhao et al. reported associations with treatment response and grade 3 or 4 toxicity for rs4975605 and rs2736109 in Stage III/IV NSCLC Han Chinese patients (51). Overall, rs4975605-
CA genotype was associated with a higher likelihood of non-response (OR=1.51, 95% CI=1.01-2.25, p=0.046), especially among females (p=1.57×10^{-4}), never-smokers (p=1.94×10^{-4}), never-smoking females (p=1.40×10^{-4}), and Stage IV patients (p=0.003). An increased, but not statistically significant risk of gastrointestinal toxicity was observed for rs2736109-GA (OR=1.68, 95% CI=0.99-2.83).

**Telomere Length: study description and methods**

Seven studies examined the prognostic role of TL in lung cancer, six of which were restricted to NSCLC (Supplementary Table S2). One cohort study did not report the histology distribution (48). Studies were varied in terms of their geographical locations and participant ethnicity. There were three studies conducted in Asian patients from Korea (55), Taiwan (56) and Japan (57), two North American studies with predominantly (>80%) Caucasian patients, and two European studies carried out in Denmark (48) and Spain (58). Two studies focused exclusively on PFS, three only assessed OS, and two studies examined both outcomes. All but one were observational studies. The exception was an open-label randomized phase II clinical trial of imetelstat, a telomerase inhibitor (59). The primary end point of this study was PFS among patients with non-progressive, advanced NSCLC, after platinum-based doublet chemotherapy (59). In the context of this trial, TL was investigated as a predictive biomarker for imetelstat activity. The efficacy of therapy with imetelstat was examined in stratified analyses among patients grouped into the shortest 1/2, shortest 1/3, and shortest 1/4 of tumor TL (59).

Two of the six observational studies were cohorts investigating factors related to cancer risk and progression, where TL was measured in peripheral blood leukocytes (PBL). Weischer et al. evaluated lung cancer patients identified from a 20-year prospective follow-up of a population-based sample of 47102 individuals in Denmark (48). Kim et al. collected information from 467 lung cancer patients enrolled at MD Anderson Cancer Center in Houston, Texas (60). PBL are the most common tissue of choice for measuring TL in studies that involve cancer-free individuals, and are considered to be an acceptable surrogate for TL in other tissues or organs of interest. In contrast, tumor TL can be more heterogeneous and reflect the cumulative impact of many tumor-associated factors that influence telomere homeostasis. Both studies using PBL collected samples prior to treatment, and Weischer et al. obtained blood prior to cancer diagnosis (48, 60). Therefore, the findings of these studies are unlikely to be confounded by treatment.

The remaining observational studies and clinical trial are best characterized as case-series selected using hospital-based sampling, such as patients undergoing resection, who were subsequently followed up for disease recurrence and mortality. These five studies evaluated tumor specimens.
The method of DNA extraction was not reported in two studies. QIAamp was used in 3 studies (including both cohorts), and two studies used organic extraction with Phenol/Chloroform. Direct comparison of these methods (61) found that DNA isolated by organic extraction produced consistently similar TL results, whereas QIAamp produced shorter estimates for RTL and a restricted range of TL variance, suggesting that studies using QIAamp may be vulnerable to type II error.

There was variability in the methods used to measure TL, which represents an important source of heterogeneity between studies (62, 63). All approaches have their own limitations. Methods that start with genomic DNA include the Southern blot telomeric restriction fragment (TRF) analysis and quantitative polymerase chain reaction (qPCR). Another set of methods relies on fluorescent in situ hybridization (FISH) to detect telomere repeats in individual cells or chromosomes.

TRF was used in three studies. It analyzes TL either as a ratio of length in tumor samples to paired normal tissue, or in absolute lengths. The most significant drawback of TRF is the requirement for substantial amounts of DNA (1.5-10 μg, minimum 105 cells), which often precludes its use in archival biopsy tissues, where DNA can be degraded or scarce (63, 64). TRF may slightly overestimate TL by including reads from the sub-telomeric regions, and has a lower sensitivity for very short telomeres, since there is a threshold below which a hybridization signal will not be produced (62, 63). However, despite these limitations the measurement error of the TRF assay is low, making it a method of choice in many studies.

In studies where hundreds or thousands of blood samples require testing, q-PCR methods are the only high-throughput strategy available (63, 64). Although not as precise as TRF, a recent extension of the traditional qPCR, the monochrome multiplex q-PCR (MM-qPCR), has improved accuracy and allows absolute TL (ATL) to be estimated (65). Four studies used q-PCR methods and two employed the MM-qPCR assay.

FISH methods, used in the intelestat trial to validate qPCR techniques (59), can also provide highly accurate TL measurements within single cells, however these assays require large amounts of viable DNA, requiring that samples be processed promptly after collection and making these methods sensitive to proper DNA collection and storage (63, 64). Similarly to TRF, because FISH methods use hybridization, there will be a threshold below which TL measurement will not be possible. This method was only feasible in the context of a prospective study or trial.

*Telomere Length: overall survival*
Associations differed across the 3 studies that investigated the role of TL in OS (Table 4). Two studies linked shorter TL to poor survival outcomes. A large population-based, prospective cohort from Denmark found that among 522 lung cancer patients, those experiencing increased telomere attrition had a higher risk of death (HR per 1000 bp decrease in TL: 1.27, 95% CI=1.13–1.43). This study did not examine associations by lung cancer histology, or any other relevant subgroups. Similar results were observed by Jeon et al., in a study of tumor samples from 164 Korean NSCLC patients (55). Significantly higher mortality was observed for patients in the shortest quartile of RTL compared to all others (HR=2.67, 95% CI=1.50–4.75). This association was observed for both adenocarcinoma and squamous cell carcinoma (55). The association between shorter TL and poor survival outcomes was more pronounced for Stage I (HR=5.41, 95% CI=2.40–12.2), compared to Stage II-IIIa disease (HR=1.51, 95% CI=0.58–3.92), as well as among current smokers (HR=3.28, 95% CI=1.64–6.56).

In contrast, a study by Hsu et al., which examined TL in paired tumor and normal tissues (T/N ratio) in 79 Stage I-IV NSCLC patients, observed improved OS in individuals with shorter TL and higher mortality in those with longer or “maintained” TL, defined as T/N>0.75 (56). This study observed improved 4-year cumulative survival among patients with T/N≤0.75 (69.2%), compared to T/N>0.75 (41.3%; p=0.0227). Using T/N≤0.75 as the reference category, they observed higher mortality among patients with TL maintenance (HR for T/N>0.75: 2.54, 95% CI=1.21–5.32) (56).

The study by Hirashima et al. adopted a hypothesis that extreme increases or decreases in TL in tumors when compared with normal tissues are associated with poorer OS. This study used TRF to compare TL in tumor and paired normal tissues of 72 Stage I-III NSCLC patients (57). In normal tissues, TL expressed as mean ± standard deviation (SD) was 6.2±1.1 kb (57). These authors defined bi-directional TL alterations as TL outside the mean ± 2 SD range of values observed for normal tissues (8.4 kb to 4.0 kb)(57). Significantly shorter survival durations were observed in the 25 patients (34.7%) with TL alterations, confirmed on multivariate analysis, demonstrating poorer OS among patients with altered TL (HR=3.05, 95% CI=1.46–6.36) (57).

The telomerase inhibitor trial examined PFS in patients stratified by TL (59). Although these differences did not reach statistical significance, the effect of imetelstat on preventing cancer recurrence was largest among patients in the 1/3 shortest TL group (HR=0.43, 95% CI=0.14–1.3). The median PFS in the short TL group treated with imetelstat increased to 1.9 months, compared to 1.5 months in the control arm (59). Patients with short TL who were treated with imetelstat were the only group where the cumulative survival rate remained above 50%.

*Telomere Length: disease recurrence and progression*
Definitions of PFS were very similar among the 3 observational studies of TL, although only Kim et al. (60) specified which sites were included in the recurrence definition. All 3 studies reported statistically significant associations between TL and cancer recurrence, however the HRs were in opposing directions (Table 5). A prospective follow-up of 473 NSCLC patients found that longer leukocyte TL was associated with a higher likelihood of recurrence (HR=1.75, 95% CI=0.96–3.22) (60). Although the main effects analysis did not reach statistical significance, the HR for longer TL was statistically significant for females with adenocarcinoma (HR=2.67, 95% CI=1.19–6.03) (60). In contrast, studies using tumor DNA found telomere shortening to be associated with cancer recurrence (43,46). Frias et al. measured TL using TRF in 77 Spanish NSCLC patients, and observed a higher likelihood of recurrence among patients with shorter TL (HR=1.89, 95% CI=1.15–3.10) (58). Jeon et al. observed poorer PFS among patients in the lowest quartile of tumor TL (HR=1.92, 95% CI=1.17–3.14)(55). Similar to the findings for OS, the likelihood of cancer recurrence was greater among Stage I (HR=2.71, 95% CI=1.39–5.29) compared to Stage II-IIIA (HR=1.31, 95% CI=0.60–2.84) patients and smokers (HR=2.30, 95% CI=1.27–4.15) (55).

The imetelstat trial did not observe any statistically significant differences in PFS between short and long TL strata (59). However, similar to findings for OS, there appeared to be a PFS trend towards a numerically larger treatment benefit among patients with short TL (HR=0.43, 95% CI=0.14–1.30), compared to those with medium/long TL (HR=0.86, 95% CI=0.39–1.88)(59).

Discussion

Lung cancer contributes to nearly 20% of all cancer deaths (1, 2). Advances in molecular biology and epidemiology can identify accurate and reliable biomarkers and improve stratification of the patients into more precise groups to assist in selection of optimal treatment modalities, as have been seen in the case of EGFR mutations and ALK rearrangements. Targets of interest currently include KRAS, PIK3CA, ROS1, and BRAF mutations (66, 67). TL has been an area of growing interest, as new agents are being evaluated targeting telomerase (59, 68, 69), while the 5p15.33 region, known to be important in lung cancer development, contains an important telomerase regulatory gene, TERT. In addition, CLPTM1L, located in the same genetic region, has been associated with cisplatin-induced apoptosis (23). Cisplatin and platinum agents have been the cornerstone of chemotherapeutic management of lung cancers, even though only a third of patients have tumor shrinkage with its use (70). Thus the prognostic and predictive role of TL and 5p15.33 region polymorphisms on survival and response to platinum-based therapy is of great interest. Our synthesis of current evidence for lung cancer uncovers some promising leads and demonstrates potential clinical applications of telomere length and 5p15.33 genetic profiles.
Of the studies focusing on genetic variants in the 5p15.33 region, significant associations with both OS and PFS were reported for rs4975616-A (TERT-CLPTM1L) and rs401681-T (CLPTM1L). However, while rs4975616-A was only investigated in one study (50), the evidence across three studies of rs401681-T was conflicting. One study reported poorer OS among SCLC patients (52), another observed improved OS for NSCLC (46), while a third study of rs401681-T in NSCLC patients reported no association (50). Variants that were predictive of OS in at least one study included rs2735940-T (TERT) and rs402710-T (CLPTM1L). In addition, rs2736109-A (TERT) was associated with PFS. Although only two SNPs, rs401681 and rs402710-T, were analyzed in more than one study, most of the variants discussed in this review are located in a 62-kb linkage disequilibrium (LD) block including the 5′-end of TERT, its promoter, and the entirety of CLPTM1L. Both rs402710-C and rs4975616-A are in strong LD with rs401681-C in European (R²=1.0 and R²=0.87) and Chinese and Japanese (R²=0.88 and R²=0.42) populations.

Although the findings for 5p15.33 variants are sparse and conflicting, partly due to a limited number of studies with modest sample sizes, the biological significant of TERT/CLPTM1L and the genetic architecture of this region suggest that 5p15.33 may harbor other variants that could play a role in OS and PFS, as this region appears to be under strong evolutionary constraint and shows relatively little common genetic variation (71). Some functional evidence exists for rs2736109 and rs2735940, both in the TERT promoter region. Rs2736109 is localized in GATA-2 transcription factor binding site, and rs2735940 is associated with higher transcriptional and telomerase activity, and longer TL (51, 72). Rs401681 has also been associated with TL, but not with TERT activity (73). These observations point to TERT activity and TL regulation as potentially relevant mechanisms in mediating the associations with clinical outcomes in lung cancer.

Our review suggests that the relationship between TL and prognosis is complex and non-linear. Firstly, differences in the underlying biological processes that are reflected in tumor and blood TL make it challenging to synthesize the associations across these studies. It remains unclear whether the TL abnormalities that are observed in blood are reflective of underlying genetic susceptibility, or arise as a consequence of the carcinogenic process, or possibly both. The type of telomere dysfunction that is a more robust predictor of clinical outcomes may also vary by tumor histology and tissue under investigation. Studies measuring leukocyte TL using qPCR offered somewhat conflicting messages, but inconsistencies were also observed among the studies investigating tumor TL measured using the Southern blot TRF assay. Thus, contrasting findings may not be easily explained by differences in tissue or method of TL measurement.
Secondly, contrasting results highlight potential different mechanisms acting under different circumstances. Several studies hypothesize that telomeric shortening promotes genomic instability. With the concurrent inactivation of key tumor suppressor genes such as p53 and/or p16/Rb, a cellular environment may be created that facilitates the acquisition of necessary properties for metastasis and recurrent disease. Conclusions from the PBL study of Weischer et al. (48) and tumor studies by Jeon et al. (55) and Frias et al. (58) are consistent with shorter TL being associated with shorter OS and PFS.

In contrast, longer TL may reflect telomerase reactivation, which promotes tumor growth and immortalization. Therefore, longer TL may be a marker for the acquired enhanced proliferative and survival capacity of malignant cells, which would in turn translate to more aggressive disease. Longer TL may allow for more actively reproducing cells, leading to an accumulation of mutations affecting apoptosis and senescence pathways, and increase the number of viable tumor cells (60, 74). Additionally, the sustained replication of unstable tumor cells with longer TL may allow for somatic evolution, such as the acquisition of mutations that contribute to the emergence of clones with enhanced capacity for invasion and metastasis (43, 75, 76). This theory fits with the results reported by the Caucasian-predominant study of Kim et al. (60), particularly in, females with adenocarcinoma, and in the study of Chinese patients in Hsu et al. (56), which also observed adverse survival outcomes in patients with a higher T/N ratio (>0.75).

To complicate matters, EGFR mutations and ALK rearrangements are found in higher proportions in never-smoking patients, while EGFR mutations are associated with being female, of East Asian descent, and having adenocarcinoma (67, 77, 78). Could mechanisms driven by different mutations such as EGFR be responsible for differences in the opposing relationships between TL and OS? This hypothesis is supported by the observation that EGF activates telomerase through up regulation of TERT transcription (79), however, there are no studies directly investigating TL and TERT in specific subgroups of patients by mutational status. The bidirectional findings in Japanese patients by Hirashima et al. (57) and decreased OS and PFS in Korean smokers by Jeon et al. (55) are consistent with this theory of alternative mechanisms, however, these studies did not report EGFR or KRAS mutation status. In fact, of all the publications reviewed here, only de Mello et al. (46) and Chiappori et al. (59) reported the number of patients positive for EGFR or KRAS mutations, however, associations with TL were not investigated in these subgroups.

Therefore, it is possible that different aspects of telomere dysfunction may be driven by somatic molecular alterations. Telomere elongation may be an indicator of the immortality of
tumor cells (a finding intriguing since it was found in subsets of adenocarcinomas, females, and populations of East Asian descent where \textit{EGFR} mutations are common), whereas extremely shortened TL in malignant cells may be a marker for aggressive tumors marked by increased genomic instability, where genomic instability is a hallmark of smoking related lung cancer (43, 80). Data from the Cancer Genome Atlas and other sources supports the contention that smoking-related lung cancers have many-fold increases in their mutational landscape, when compared with those with \textit{EGFR} mutations (67, 77).

Also intriguing are the observations from the telomerase inhibitor trial (59). Although this small sample analysis should be considered a negative result given a lack of statistical significance, the results are suggestive of a greater clinical benefit from telomerase inhibition in patients with tumors possessing shorter TL, in a sample with unknown smoking prevalence but a low prevalence (10\%) of \textit{EGFR}-positive patients. Furthermore, since telomerase preferentially elongates shorter telomeres (81), it is plausible that blocking its activity confers a larger benefit in the short TL subgroup.

However, despite promising leads offered by the studies in this review, there are several important methodological caveats that should be acknowledged. Firstly, low statistical power is one of the most significant limitations shared by the studies in this review. With the exception of three reports (47, 48, 52), most lacked sufficient power to detect modest associations with OS and PFS that would be expected for common genetic variants and TL. Secondly, although studies of candidate polymorphisms had the benefit of being hypothesis-driven and limited the number of comparisons, this approach may miss associations for rare and low-frequency variants, and those that were not chosen based on previous GWAS of lung cancer risk. Thirdly, strong and consistent evidence across multiple studies, and validation in different patient sub-populations with respect to stage, histology, and ethnicity, smoking status, mutational status, is still lacking in the literature linking genetic variants to clinical outcomes in lung cancer. Fourthly, functional studies are also needed to help characterize the specific biological pathways through which these SNPs may impact lung cancer recurrence and survival.

For studies of TL, additional methodological concerns require discussion. Firstly, no attempts were made to refine the associations by cell type, despite the fact that leukocyte TL is an average across all immune cell subpopulations present in blood, and may obscure important differences in their TL dynamics. Secondly, there is no accepted range of normal TL in healthy tissues, therefore tumor studies that use the T/N ratio and define TL alterations based on departure from values observed in one group may not be applicable to other patient populations. Thirdly, using the T/N ratio to predict survival outcomes may not take into account molecular
features of the tumor that could be effect modifiers of the relationship between TL and outcome (55). Fourthly, low power in small case series may be exacerbated by methods of TL measurement that have low sensitivity and are prone to measurement error. Lastly, the impact of accelerated telomere attrition resulting from the psychological impact of a cancer diagnosis should be considered, since TL measured after diagnosis may also reflect an increased emotional and physical burden (80, 82).

Future studies can be improved with the use of repeated measurements to better ascertain temporal changes in TL that are associated with clinical outcomes. The presence of intra-tumor heterogeneity resulting from diverse evolution processes (83, 84), also suggests that examining TL in multiple tissue samples may be informative. Other methodological concerns include inconsistent reporting of basic characteristics such as smoking status, ethnicity, as well clinically relevant markers and mutation profiles. None of the genetic association studies carried out an analytic adjustment for the underlying population structure, and instead relied on self-reported ethnicity, or inferred ethnicity based on patient residence. Although confounding by population stratification is more important for genetic association studies, this should also be considered for studies of TL, since it may vary between ethnic groups (85).

Taken together, the current body of literature offers some encouraging, yet inconsistent findings that continue to support interest in 5p15.33 genetic variants and telomere length as biomarkers with potential clinical utility – not only for prognostication, but also as a potential lung cancer treatment targets. However, the limited number of studies and their methodological limitations leave more unanswered questions than firm conclusions, and highlight the need for larger, carefully designed studies with clinically defined subpopulations of lung cancer patients and refined, high-resolution genetic analyses. Leveraging information on relevant biological pathways and telomere function in order to disentangle complex associations, will enhance our ability to, uncover findings that may be translated into improved prognostic assessment and treatment approaches. By first studying the associations across specific tumor sites such as lung cancer, one can further understand the potential interactions between these biomarkers with clinical, demographic and molecular factors.
References

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Table 1: Associations between 5p15.33 genetic variants and overall survival (OS) in lung cancer patients

<table>
<thead>
<tr>
<th>SNP (Gene)</th>
<th>Study [Ref]</th>
<th>Minor Allele</th>
<th>Sample Size (Events)</th>
<th>Genetic Model</th>
<th>Analysis</th>
<th>Effect Estimate (95% CI)</th>
<th>P-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2735940 (TERT)</td>
<td>Catarino et al. (2010) [49]</td>
<td>T</td>
<td>174 cases (58)</td>
<td>Recessive</td>
<td>Cox Regression</td>
<td>HR 0.52 (0.35–0.77)</td>
<td>0.001</td>
<td>Improved OS</td>
</tr>
<tr>
<td>rs2736098 (TERT)</td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.14 (0.97–1.28)</td>
<td>0.14</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs2736100 (TERT)</td>
<td>Li et al. (2014) [52]</td>
<td>C</td>
<td>874 cases (521)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.94 (0.83–1.07)</td>
<td>0.376</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs2853677 (TERT)</td>
<td>Li et al. (2014) [52]</td>
<td>G</td>
<td>874 cases (521)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.92 (0.81–1.04)</td>
<td>0.184</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs2853677 (TERT)</td>
<td>Li et al. (2014) [52]</td>
<td>G</td>
<td>874 cases (521)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.92 (0.81–1.04)</td>
<td>0.184</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs31489 (CLPTM1L)</td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.029</td>
</tr>
<tr>
<td>rs401681 (CLPTM1L)</td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.92 (0.79–1.03)</td>
<td>0.09</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>Li et al. (2014) [52]</td>
<td>T</td>
<td>874 cases (521)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.34 (1.22–1.47)</td>
<td>0.0001</td>
<td>Poorer OS</td>
</tr>
<tr>
<td></td>
<td>Li et al. (2014) [52]</td>
<td>T</td>
<td>874 cases (521)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.33 (1.20–1.47)</td>
<td>0.0001</td>
<td>Poorer OS</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.99 (0.87–1.11)</td>
<td>0.71</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>Xun et al. (2011) [47]</td>
<td>T</td>
<td>1094 cases (874)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.07 (0.97–1.19)</td>
<td>0.18</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>Xun et al. (2011) [47]</td>
<td>T</td>
<td>673 cases (537)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.12 (0.98–1.28)</td>
<td>0.11</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>Xun et al. (2011) [47]</td>
<td>T</td>
<td>673 cases (537)</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>SHR 1.10 (0.97–1.26)</td>
<td>0.14</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.309</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.958</td>
</tr>
<tr>
<td></td>
<td>Xun et al. (2011) [47]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.337</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>SNP (TERT-CLPTM1L)</th>
<th>Reference</th>
<th>Major Allele</th>
<th>Sample Size</th>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs465498 (CLPTM1L)</td>
<td>Li et al. (2014) [52]</td>
<td>G</td>
<td>874 cases (521)</td>
<td>Log additive Cox Regression</td>
<td>HR 1.08 (0.90–1.28)</td>
<td>0.4148</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs4975616 (TERT-CLPTM1L)</td>
<td>Azad et al. (2014) [50]</td>
<td>A</td>
<td>564 cases</td>
<td>Log additive Cox Regression</td>
<td>HR 0.75 (0.69–0.91)</td>
<td>0.002</td>
<td>Improved OS</td>
</tr>
</tbody>
</table>

1 rs2735940 (hTERT -1327 C/T): Minor allele is C
2 rs402710: Minor allele is C

**Abbreviations:** Ref: reference citation number; SNP (Single nucleotide polymorphism); OS (Overall survival); HR (Hazard ratio); SHR (Sub-hazard ratio from a competing risks model)
Table 2: Associations between 5p15.33 genetic variants and progression-free survival (PFS) or disease recurrence in lung cancer patients

<table>
<thead>
<tr>
<th>SNP (Gene)</th>
<th>Study [Ref]</th>
<th>Minor Allele</th>
<th>Sample Size (Events)</th>
<th>Genetic Model</th>
<th>Analysis</th>
<th>Effect Estimate (95% CI)</th>
<th>P-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2736098 (TERT)</td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 1.18 (0.98–1.34)</td>
<td>0.08</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs2736109 (TERT)</td>
<td>Zhao et al. (2015) [51]</td>
<td>A</td>
<td>896 cases (558 events)</td>
<td>Heterozygotic</td>
<td>Cox Regression</td>
<td>HR 0.88 (0.74–1.06)</td>
<td>0.171</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Homozygotic</td>
<td>Cox Regression</td>
<td>HR 1.23 (0.95–1.60)</td>
<td>0.122</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Best-fitting&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Cox Regression</td>
<td>HR 1.32 (1.03–1.68)</td>
<td>0.026</td>
</tr>
<tr>
<td>rs31489 (CLPTM1L)</td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.588</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dominant</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rs401681 (CLPTM1L)</td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.86 (0.76–0.99)</td>
<td>0.04</td>
<td>Improved PFS</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dominant</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rs402710 (CLPTM1L)</td>
<td>Azad et al. (2014) [50]</td>
<td>T</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.92 (0.78–1.05)</td>
<td>0.12</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.269</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dominant</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rs4635969 (TERT-CLPTM1L)</td>
<td>De Mello et al. (2013) [46]</td>
<td>T</td>
<td>144 cases</td>
<td>Genotypic</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
<td>0.665</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recessive&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Log-rank test</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rs4975616 (TERT-CLPTM1L)</td>
<td>Azad et al. (2014) [50]</td>
<td>A</td>
<td>564 cases</td>
<td>Log additive</td>
<td>Cox Regression</td>
<td>HR 0.74 (0.62–0.89)</td>
<td>0.001</td>
<td>Improved PFS</td>
</tr>
</tbody>
</table>

<sup>1</sup> Longest median disease-free survival time was observed for rs2736109-GA individuals

<sup>2</sup> Shortest median disease-free survival time was observed for rs2736109-AA individuals

<sup>3</sup> Stratification analyses by patient characteristic subgroups were performed and the most significant genetic model was assumed as the best fitting model

<sup>4</sup> Longest median disease-free survival time observed for rs401681-TT individuals

<sup>5</sup> rs402710: Minor allele is C

**Abbreviations:** Ref: reference citation number; SNP (Single nucleotide polymorphism); PFS (Disease-free survival); HR (Hazard ratio)
<table>
<thead>
<tr>
<th>SNP (Gene)</th>
<th>Study [Ref]</th>
<th>Patient Therapy</th>
<th>Outcome</th>
<th>Minor Allele</th>
<th>Sample Size (Events)</th>
<th>Genetic Model</th>
<th>Analysis</th>
<th>Effect Estimate (95% CI)</th>
<th>P-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10073340 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>T</td>
<td>112 cases (35)</td>
<td>Log additive</td>
<td>Logistic Regression</td>
<td>OR 1.91 (0.39–9.36)</td>
<td>0.349</td>
<td>Not associated</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>CC: 100 cases (33)</td>
<td>Genotypic</td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>2.00 (0.39–10.3)</td>
<td>0.335</td>
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<tr>
<td></td>
<td></td>
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<td>TC: 12 cases (2)</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.18 (0.99–2.83)</td>
<td>0.054</td>
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<td></td>
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<td>AA: 122 cases (9)</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.27 (0.57–2.86)</td>
<td>0.560</td>
<td></td>
</tr>
<tr>
<td>rs2736109 (TERT)</td>
<td>Zhao et al. (2015) [51]</td>
<td>Stage IIIA/IV NSCLC: cisplatin- navelbine, cisplatin-gemcitabine, cisplatin-paclitaxel</td>
<td>Severe toxicity: Gastrointestinal</td>
<td>A</td>
<td>GG: 388 cases (6)</td>
<td>Genotypic</td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.29 (0.94–1.78)</td>
<td>0.120</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>GA: 459 cases (124)</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>0.78 (0.46–1.32)</td>
<td>0.348</td>
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<tr>
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<td></td>
<td>AA: 122 cases (22)</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.68 (0.99–2.83)</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>rs31484 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>T</td>
<td>113 cases (15)</td>
<td>Log additive</td>
<td>Logistic Regression</td>
<td>OR 1.56 (0.53–4.57)</td>
<td>0.312</td>
<td>Not associated</td>
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<td></td>
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<td></td>
<td></td>
<td>CC: 48 cases</td>
<td>Genotypic</td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.10 (0.77–1.61)</td>
<td>0.641</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>CA: 71 cases</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.10 (0.77–1.61)</td>
<td>0.641</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>AA: 25 cases</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.10 (0.77–1.61)</td>
<td>0.641</td>
<td>Not associated</td>
</tr>
<tr>
<td>rs380286 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>A</td>
<td>113 cases (15)</td>
<td>Log additive</td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.56 (0.53–4.57)</td>
<td>0.312</td>
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<tr>
<td></td>
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<td></td>
<td>GG: 90 cases (30)</td>
<td>Genotypic</td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.65 (0.53–5.13)</td>
<td>0.283</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GA: 23 cases (5)</td>
<td></td>
<td>Logistic Regression</td>
<td>OR 1</td>
<td>1.65 (0.53–5.13)</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>rs401681 (CLPTM1L)</td>
<td>De Mello et al. (2013) [46]</td>
<td>Advanced NSCLC: gefitinib (EGFR+), platinum-based (EGFR-)</td>
<td>Response rate: Undefined</td>
<td>T</td>
<td>CC: 40 cases</td>
<td>CT: 77 cases</td>
<td>TT: 27 cases</td>
<td>CT+TT: 104 cases</td>
<td>Genotypic Logistic Regression</td>
<td>OR</td>
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<tr>
<td>rs402710 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>T</td>
<td>113 cases (35)</td>
<td>CC: 57 cases (19)</td>
<td>TC: 50 cases (15)</td>
<td>TT: 6 cases (1)</td>
<td>Genotypic Logistic Regression</td>
<td>OR</td>
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<tr>
<td>rs421629 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>T</td>
<td>113 cases (15)</td>
<td>CC: 58 cases (19)</td>
<td>TC: 49 cases (15)</td>
<td>TT: 6 cases (1)</td>
<td>Genotypic Logistic Regression</td>
<td>OR</td>
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<tr>
<td>rs451360 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>T</td>
<td>109 cases (35)</td>
<td>CC: 87 cases (29)</td>
<td>TC: 26 cases (6)</td>
<td>GT: 13 cases (4)</td>
<td>Log additive Logistic Regression</td>
<td>OR</td>
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<tr>
<td>rs4635969 (TERT-CLPTM1L)</td>
<td>De Mello et al. (2013) [46]</td>
<td>Advanced NSCLC: gefitinib (EGFR+), platinum-based (EGFR-)</td>
<td>Response rate: Undefined</td>
<td>T</td>
<td>CC: 94 cases</td>
<td>CT: 44 cases</td>
<td>TT: 6 cases</td>
<td>CT+TT: 50 cases</td>
<td>Genotypic Logistic Regression</td>
<td>OR</td>
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<tr>
<td>rs467095 (CLPTM1L)</td>
<td>Liang et al. (2014) [53]</td>
<td>Stage III/IV lung, cisplatin</td>
<td>Response rate: SD/PD vs. CR/PR</td>
<td>G</td>
<td>AA: 87 cases (29)</td>
<td>AG: 17 cases (3)</td>
<td>GG: 5 cases (3)</td>
<td>Genotypic Logistic Regression</td>
<td>OR</td>
<td>0.83 (0.34-2.04)</td>
</tr>
<tr>
<td>rs4975605  (TERT)</td>
<td>Zhao et al. (2015) [51]</td>
<td>AG+GG: 22 cases (6)</td>
<td>Dominant</td>
<td>OR 1.14 (0.38–3.42) 0.586</td>
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<td></td>
<td></td>
<td>CC: 795 cases (651)</td>
<td>Genotypic</td>
<td>Logistic Regression</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CA: 168 cases (125)</td>
<td></td>
<td>OR 1.51 (1.01–2.25) 0.046</td>
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<td></td>
<td></td>
<td>AA: 12 cases (11)</td>
<td></td>
<td>OR 0.41 (0.05–3.26) 0.402</td>
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<tr>
<td></td>
<td></td>
<td>CA+AA: 180 cases (136)</td>
<td>Dominant</td>
<td>OR 1.42 (0.95–2.11) 0.085</td>
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</tr>
</tbody>
</table>

**Clinical benefit: PD vs. CR/PR/SD**

**Stage IIIA/IV NSCLC: cisplatin-navelbine, cisplatin-gemcitabine, cisplatin-paclitaxel**

**Severe toxicity: Gastrointestinal**

- CC: 784 cases (66)
- CA: 168 cases (13)
- AA: 12 cases (1)

**Severe toxicity: Hematological**

- CC: 789 cases (195)
- CA: 168 cases (32)
- AA: 12 cases (5)

**Severe toxicity: Neutropenia**

- CC: 762 cases (101)
- CA: 162 cases (13)
- AA: 11 cases (1)

**Severe toxicity: Anemia**

- CC: 772 cases (23)
- CA: 161 cases (5)
- AA: 11 cases (1)

**Severe toxicity: Thrombocytopenia**

- CC: 777 cases (30)
- CA: 162 cases (3)
- AA: 11 cases (1)

**Severe toxicity: Gastrointestinal**

- CC: 784 cases (66)
- CA: 168 cases (13)
- AA: 12 cases (1)

**Severe toxicity: Hematological**

- CC: 789 cases (195)
- CA: 168 cases (32)
- AA: 12 cases (5)

**Severe toxicity: Neutropenia**

- CC: 762 cases (101)
- CA: 162 cases (13)
- AA: 11 cases (1)

**Severe toxicity: Anemia**

- CC: 772 cases (23)
- CA: 161 cases (5)
- AA: 11 cases (1)

**Severe toxicity: Thrombocytopenia**

- CC: 777 cases (30)
- CA: 162 cases (3)
- AA: 11 cases (1)

**Severe toxicity: Gastrointestinal**

- CC: 784 cases (66)
- CA: 168 cases (13)
- AA: 12 cases (1)

**Severe toxicity: Hematological**

- CC: 789 cases (195)
- CA: 168 cases (32)
- AA: 12 cases (5)

**Severe toxicity: Neutropenia**

- CC: 762 cases (101)
- CA: 162 cases (13)
- AA: 11 cases (1)

**Severe toxicity: Anemia**

- CC: 772 cases (23)
- CA: 161 cases (5)
- AA: 11 cases (1)

**Severe toxicity: Thrombocytopenia**

- CC: 777 cases (30)
- CA: 162 cases (3)
- AA: 11 cases (1)

---

1 Severe treatment toxicity defined as Grade 3 or 4 toxicity based on NCI Common Toxicity Criteria v. 3.0

**Abbreviations:** Ref: reference citation number; SNP (Single nucleotide polymorphism); OR (Odds ratio); NSCLC (Non-small cell lung cancer); EGFR (Epidermal growth factor receptor); RECIST (Response Evaluation Criteria in Solid Tumor Group); RECIST outcomes: CR (Complete Response), PR (Partial Response); SD (Stable Disease); PD (Progressive Disease); NCI (National Cancer Institute)
<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Sample Size (Events)</th>
<th>Variable</th>
<th>Analysis</th>
<th>Effect Estimate (95% CI)</th>
<th>P-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weischer et al. (2013) [48]</td>
<td>522 cases (468)</td>
<td>ATL – Continuous (T/S)</td>
<td>Cox Regression</td>
<td>HR per 1000 bp decrease 1.27 (1.13–1.43)</td>
<td>-</td>
<td>Shorter TL → poorer OS</td>
</tr>
<tr>
<td>Jeon et al. (2012) [55]</td>
<td>164 cases (58)</td>
<td>RTL – Quartiles (T/S)</td>
<td>Cox Regression</td>
<td>4th: HR 1.00</td>
<td></td>
<td>Shorter TL → poorer OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3rd: HR 0.69 (0.31–1.53)</td>
<td>0.37</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd: HR 0.73 (0.32–1.62)</td>
<td>0.43</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st: HR 2.14 (1.06–4.35)</td>
<td>0.03</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Others: HR 1.00</td>
<td></td>
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</tr>
<tr>
<td>Hsu et al. (2004) [56]</td>
<td>79 cases</td>
<td>RTL – Dichotomous (T/N)</td>
<td>Cox Regression</td>
<td>HR T/N≤0.75: RR 1.00</td>
<td>0.014</td>
<td>Maintained TL → poorer OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T/N&gt;0.75: HR 2.54 (1.21–5.32)</td>
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</tr>
<tr>
<td>Hirashima et al. (2000) [57]</td>
<td>72 cases</td>
<td>ATL – Dichotomous (Outside normal range)</td>
<td>Cox Regression</td>
<td>HR Normal: HR 1.00</td>
<td>0.0033</td>
<td>Abnormal TL → poorer OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Altered: HR 3.046 (1.46–6.36)</td>
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</tr>
<tr>
<td>Chiappori et al. (2014) [59]</td>
<td>19 cases (15)</td>
<td>RTL – Dichotomous (T/S)</td>
<td>Cox Regression</td>
<td>HR Control: HR 1.00</td>
<td>-</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short: 33rd percentile</td>
<td></td>
<td>Treatment: HR 0.41 (0.11–1.46)</td>
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<tr>
<td></td>
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<td>Long: 66th percentile</td>
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<td></td>
<td></td>
<td>HR Control: HR 1.00</td>
<td>-</td>
<td>Not associated</td>
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<tr>
<td></td>
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<td></td>
<td>Treatment: HR 0.51 (0.20–1.28)</td>
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<tr>
<td></td>
<td></td>
<td>ATL – Dichotomous (T/S)</td>
<td>Cox Regression</td>
<td>HR Control: HR 1.00</td>
<td>-</td>
<td>Not associated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short: 33rd percentile</td>
<td></td>
<td>Treatment: HR 0.44 (0.11–1.87)</td>
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<tr>
<td></td>
<td></td>
<td>Long: 66th percentile</td>
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</tr>
</tbody>
</table>

**Abbreviations:** Ref: reference citation number; TL (Telomere length); OS (Overall survival); HR (Hazard ratio); RR (Relative risk); ATL (Absolute telomere length); RTL (Relative telomere length); T/S (Ratio of telomere copy number vs. single gene copy number); T/N (Ratio of TL in tumor samples vs. paired normal tissue)
Table 5: Association between telomere length (TL) and disease-free survival (PFS) or disease recurrence in lung cancer patients

<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Sample Size (Events)</th>
<th>Variable</th>
<th>Analysis</th>
<th>Effect Estimate (95% CI)</th>
<th>P-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2014)</td>
<td>473 cases (151)</td>
<td>RTL – Continuous (T/S)</td>
<td>Cox Regression</td>
<td>HR per 1 unit increase 1.75 (0.96–3.22)</td>
<td>0.07</td>
<td>Longer TL → poorer PFS</td>
</tr>
<tr>
<td>Jeon et al. (2012)</td>
<td>164 cases (81)</td>
<td>RTL – Quartiles (T/S)</td>
<td>Cox Regression</td>
<td>HR 4th: 1.00 3rd: 1.06 (0.55–2.08) 2nd: 1.14 (0.59–2.21) 1st: 1.97 (1.04–3.74) Others: 1.00 1st: 1.92 (1.17–3.14)</td>
<td>0.85 0.69 0.03 0.85 0.01</td>
<td>Shorter TL → poorer PFS</td>
</tr>
<tr>
<td>Frias et al. (2007)</td>
<td>77 cases</td>
<td>RTL - Dichotomous (T/N)</td>
<td>Cox Regression</td>
<td>RR T/N≥1: 1.00 T/N&lt;1: 1.887 (1.147–3.102)</td>
<td>0.012</td>
<td>Shorter TL → poorer PFS</td>
</tr>
<tr>
<td>Chiappori et al. (2014)</td>
<td>19 cases (10)</td>
<td>RTL – Dichotomous (T/S) Short: 33rd percentile</td>
<td>Cox Regression</td>
<td>HR</td>
<td>Control 1.00 Treatment 0.43 (0.14–1.30)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>38 cases (21)</td>
<td>RTL – Dichotomous (T/S) Long: 66th percentile</td>
<td></td>
<td>HR</td>
<td>Control 1.00 Treatment 0.86 (0.39–1.88)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>59 cases total</td>
<td>ATL – Dichotomous Short: 33rd percentile</td>
<td></td>
<td>HR</td>
<td>Control 1.00 Treatment 0.45 (0.14–1.48)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATL – Dichotomous Long: 66th percentile</td>
<td></td>
<td>HR</td>
<td>Not reported</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ref: reference citation number; TL (Telomere length); PFS (Disease-free survival); HR (Hazard ratio); RR (Relative risk); ATL (Absolute telomere length); RTL (Relative telomere length); T/S (Ratio of telomere copy number vs. single gene copy number); T/N (Ratio of TL in tumor samples vs. paired normal tissue)
Systematic review of genetic variation in chromosome 5p15.33 and telomere length as predictive and prognostic biomarkers for lung cancer

Linda Kachuri, Lidija Latifovic, Geoffrey Liu, et al.

Cancer Epidemiol Biomarkers Prev  Published OnlineFirst August 26, 2016.

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Supplementary Material  Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2016/08/26/1055-9965.EPI-16-0200.DC1

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.