Editorial

Subtype variation and actionability of telomere length abnormality in lung cancer

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Lung cancer has a 5-year survival rate of only 18%. Among the many studies investigating factors associated with the high mortality rate of this cancer, Doherty *et al.* (1) recently examined telomere length in *Cancer Epidemiology, Biomarkers & Prevention*.

Telomeres, repeating units at the ends of chromosomes that protect from DNA degradation, naturally shorten over time with age and trigger cell apoptosis. There are two opposing theories of association between abnormal telomere length and cancer progression: (I) that shorter than normal telomere structures increase susceptibility to genomic instability and tumour-inducing DNA aberrations; and (II) that longer telomere structures enhance cell survivability and therefore drive tumour development through increased opportunities for mutational propagation. There are multiple studies supporting both theories.

Doherty *et al.* investigated the link between shortened relative telomere length and small cell lung carcinoma (SCLC), raising interesting issues arising from differences in telomere length between lung cancer subtypes and prompting consideration of actionable outcomes for abnormal telomere length. These are discussed below.

Telomere length and lung cancer subtypes

Compared to other lung cancer subtypes, SCLC has comparatively rapid spread and growth and is therefore generally unsuitable for surgical treatment. It has lower survival compared to non-small cell lung carcinomas (NSCLCs), with the 5-year survival rate being only 6% for SCLC, compared to 20% for adenocarcinoma and 17% for squamous cell carcinoma (SCC). Doherty *et al.*'s study reports an association between shortened telomere lengths in blood DNA and mortality in SCLC, but not in adenocarcinoma, SCC or unspecified lung cancer subtypes. Another study reports short telomeres may be used as a marker for lung cancer risk, with the link more pronounced in SCLC (2). Alternatively, Doherty *et al.* previously found that long telomere lengths are associated with lung adenocarcinoma risk (3), and Yuan *et al.* (4) found an association between longer leucocyte telomeres and lung adenocarcinoma development. Wei *et al.* (5) showed differential expression of the telomerase reverse transcriptase gene in EGFR mutation positive NSCLC.

Between the multiple options of surgery, chemotherapy, radiation therapy and others, a patient's treatment plan for lung cancer can vary considerably, with successful identification of subtype-specific targets (such as EGFR for adenocarcinoma) driving decisions that may have a significant impact on a patient's survival. Multiple non-telomere studies published this year also emphasise differences between adenocarcinoma, SCC and SCLC. One of these focuses on profiling clinical and radiological characteristics of each subtype (6), which is key for current diagnosis methods. Two others offer methods for distinguishing between adenocarcinoma, SCC and SCLC by observing differential expression patterns of molecular markers (7,8). Thus, Doherty's group is highly justified in aiming to analyse telomere length and mortality by lung cancer histology, with the results further supporting the need for further subtype-specific research in lung cancer.

Is abnormal telomere length actionable?

Systemic versus local

Doherty *et al.* found no evidence of shortened telomeres in any other subtype of lung cancer, although others have reported that shorter telomere length in tumours is associated with worse overall and disease-free survival in both SCC and adenocarcinoma (9). The authors acknowledge this study and point out that somatic and germline telomere dynamics differ. In a cohort of idiopathic pulmonary fibrosis patients, there was no correlation between telomere lengths in blood and lung biopsies (10), leading to a hypothesis that the negative effects on survival may require a secondary localised factor in addition to shortened germline telomere lengths. The issue that arises is therefore: what is the most appropriate specimen type to answer questions about the role of telomere length in cancer?

Blood specimens are certainly less invasive and more easily obtainable than lung tissue or fluid specimens, and a blood marker for lung cancer would have significant implications for pre-screening susceptible cohorts. However, shortened telomere length in blood is also associated with common age-related diseases such as central obesity, poor sleep and hypertension (11). If multiple conditions are associated with telomere length—whether short or long—what treatment strategies or pre-emptive measures can be taken, given this lack of specificity?

Confounding effects

The cohort in Doherty *et al.*'s study was recruited from a larger study and included 45–69 years old heavy smokers with a ≥20 pack year history, some of which may have also had asbestos exposure, and all of whom subsequently developed lung cancer. Data for the SCLC contingent was fittingly considered by age, smoking status, sex, pack years and tumour stage in order to demonstrate significance. However, given that blood telomere length is associated with multiple conditions, is this stratification sufficient?

The authors refer to a separate study reporting that COPD patients have significantly shorter blood leucocyte telomeres than healthy controls (12) and Córdoba-Lanús *et al.* suggest that airflow limitation is associated with shortened telomere lengths (13). However, Doherty *et al.* did not report airflow and other lung function parameters, presence or absence of COPD, or other comorbidities associated with altered telomere length in their cohort. Given the long list of conditions reported to be associated with telomere length (of which the several mentioned above are only a small number of these), it would be difficult to account for all possible confounding factors. Still, the question is—what action can be taken?

Survival benefit

Treatments addressing abnormal telomere length are scarce—Gorenjak *et al.* outline telomerase activators and inhibitors as options for lengthening and shortening of telomeres respectively (14). A question commonly asked by patients with advanced disease is: How much time do I have? Whether abnormal telomere length can be acted upon or not, the answer is "not much", since the median survival times of stage III or IV SCLC cases in the shortest and longest telomere tertiles of Doherty *et al.*'s study were 6 and 10.8 months respectively. The diagnosis occurred 5.9 years (with a standard deviation of 3.9 years) post-blood collection, with associations with telomere length not as pronounced when the diagnosis was >5 years post-specimen collection—that is, undetectable until 5 years prior to a late stage diagnosis. Telomere length was also associated with all-cause mortality, and although this is a heavily biased cohort, associations were stronger in the ≤65 years age group—that is, approximately 7 years younger than the 2016 average World Bank-calculated healthy life expectancy of 72.

Given this short 5-year window for improving diagnosis time, even if treatment was available to alleviate or reverse telomere abnormality, would this be economically viable? In the case of Doherty *et al.*'s study, it specifically refers to lung cancer mortality. This is an even shorter time frame—a window of ~5 months if you could conservatively correct for the shortest (6 months) to the longest (10.8 months) tertile of telomere lengths, assuming there were no other contributing factors to accelerate telomere abnormality. While it is acknowledged that any extra time to an individual patient would be valuable—it would theoretically almost double the time between diagnosis and death in some cases, and potentially significantly more if diagnosed at an earlier stage—it would still be difficult to justify with current technology.

Final comments

This study identifies telomere length as a potential prognostic marker in SCLC. However, Gorenjak *et al.* highlight the practicalities of monitoring telomere length

for personalised medicine (14) and emphasise that given the multitude of factors that may influence length, it does not fulfil the requirements of a biomarker for any specific disease. Furthermore, in targeting shortened telomeres, will there be a risk of tipping the balance towards susceptibility to diseases associated with abnormally long telomeres—such as adenocarcinoma? Clearly, more research needs to be done on seeking additional drivers that alter the local lung environment in order to take advantage of current knowledge on the implications of abnormal telomere length.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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