Telomeres: The Long and Short of Developing Non-Hodgkin Lymphoma

Commentary on Lan et al., p. 7429

Ariela Noy

Chromosomal integrity is vital to the life span of the dividing cell. Telomeres are tandem sequences at chromosome ends that provide protection for the genetic coding material. Erosion of those ends leads to cell death. Does stabilization promote cancer? (Clin Cancer Res 2009;15(23):7114–5)

In this issue of Clinical Cancer Research, Lan and colleagues (1) use a new technique and a prospective cohort study to investigate the role of telomere length in the pathogenesis of non-Hodgkin lymphoma (NHL). Telomeres are complexes of tandem repeats of the sequence TTAGGG, which cap chromosomes in eukaryotes and some prokaryotes with noncircular DNA. They provide a solution to the end chromosome replication problem using an enzyme called telomerase. What causes this problem? All DNA polymerases function in a 5′ to 3′ direction, which means that one strand of DNA called the lagging strand is replicated in short bursts called Okazaki fragments. These fragments are initiated after a short RNA primer is attached to the lagging strand a short distance ahead of the DNA replication origin. The RNA fragments are eventually modified into DNA. However, the last RNA primer cannot be converted without a DNA strand in front of it. Without some mechanism, the RNA would be degraded and the DNA template shortened with each successive division. When too much chromosomal material is lost, the cell enters senescence, growth arrest, or apoptosis depending on its genetic background.

The telomerase complex solves this problem. Noncoding repetitive sequences cap the ends of the chromosomes. They are usually arrays of 6- to 8-bp G-rich repeats varying in length between species from 300 to 600 bp in yeast to many kilobases in humans. The telomerase is a ribonucleoprotein complex that protects the terminal chromosome ends by employing a different mechanism of DNA replication at the telomere, exploiting the telomere sequences using its own RNA template and a special reverse transcriptase. Germ cells, certain white blood cells, and cancer cells have active telomerase complexes, making them relatively long lived compared with other cells.

Nonetheless, the role of telomerase in cancer pathogenesis has been somewhat elusive. Many studies have reported that a shorter telomere length measured either in white blood cells or less frequently in buccal mucosa correlates with an increased risk of cancer. Others have suggested the reverse in breast cancer and melanoma (Table 1).

From a biologic perspective longer telomere length should allow for longer cellular survival, the accumulation of genetic mutations, and the possibility of accumulating potentially cancer promoting mutations.

As reported in this issue of Clinical Cancer Research, the strength of Lan and colleagues methodology lies in both their study cohort and their assay. In the latter, Lan modified Cawthon’s monochrome multiplex quantitative PCR (2, 3), which is highly precise and nearly perfectly correlated (Spearman \( r = 0.91 \), \( P < 0.0001 \)) with the Southern blot method of measuring telomere length. The multiplex technique overcomes pipetting variation seen with the monoplex technique and provides a dimensionless ratio in reference to a single copy gene template.

The study cohort was equally robust with nearly 30,000 Finnish male smokers recruited to a cancer prevention trial of \( \alpha \)-tocopherol, \( \beta \)-carotene, both, or placebo (4). Follow-up was reliable with 100% capture of incident NHL cases in the cancer registry. It should also be noted that the cells assayed were extracted from whole blood, therefore largely lymphocytes, and presumably a reservoir for the future NHL cells rather than a less relevant cell type such as a lymphocyte or buccal mucosa in studies of epithelial cancer in most of the reports noted above.

Although the ultimate study cohort was small with only 107 cases and an equal number of age-matched controls, Lan and colleagues found longer telomeres when studied by quartile and provide a dimensionless ratio in reference to a single copy gene template.

One potential drawback of the study design is the nature of the study cohort. The study was limited to male smokers. Few, but some, forms of lymphoma have a male predominance for unclear reasons. Thus, the results might differ somewhat in women. Also, smokers are constantly bombarded with carcinogens. Some studies have reported an increased risk of certain types of lymphoma in smokers. Thus, the effect of telomere length may have been overestimated in Lan’s study.
Overall, Lan and colleagues successfully show an increase in telomere length in circulating lymphocytes correlates with an increased risk of developing NHL. One can envision that future research might result in a multifactorial model predictive of an individual’s risk. If such an individual could then be provided targeted therapy to prevent cancer, morbidity of future disease and lives will be saved.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Table 1. Published associations between cancer risk and telomere length

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cancer type</th>
<th>Telomere length correlating with cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jang et al. (5)</td>
<td>Lung</td>
<td>Shorter</td>
</tr>
<tr>
<td>Shen et al. (6)</td>
<td>Breast</td>
<td>Shorter</td>
</tr>
<tr>
<td>Wu et al. (7)</td>
<td>Bladder, head and neck, lung and renal</td>
<td>Shorter</td>
</tr>
<tr>
<td>Widmann et al. (8)</td>
<td>NHL</td>
<td>Shorter</td>
</tr>
<tr>
<td>Broberg et al. (9)</td>
<td>Bladder</td>
<td>Shorter</td>
</tr>
<tr>
<td>Risques et al. (10)</td>
<td>Esophagus</td>
<td>Shorter</td>
</tr>
<tr>
<td>McGrath et al. (11)</td>
<td>Bladder</td>
<td>Shorter</td>
</tr>
<tr>
<td>Han et al. (12)</td>
<td>Skin</td>
<td>Longer</td>
</tr>
<tr>
<td>Svenson et al. (13)</td>
<td>Breast</td>
<td>Longer</td>
</tr>
</tbody>
</table>
Clinical Cancer Research

Telomeres: The Long and Short of Developing Non-Hodgkin Lymphoma

Ariela Noy