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Using biomarkers of aging to identify modifiable mechanisms underlying age-related risk for cancer

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A common feature of many epithelial cancers is that risk increases with older age. From the perspective of disease prevention, older age is an un-modifiable risk factor, thus age is most often treated as a nuisance confounder in epidemiologic analyses. Although age itself is not modifiable, the specific physiological changes that occur over time that increase the risk for cancer may be. Identifying the mechanisms through which age increases the risk of cancer may lead to novel opportunities for preventing disease. To use this approach, it is first necessary to study a cancer that is relatively common, has a strong association with older age, and has associations with modifiable risk factors beyond age. Next, biomarkers of aging identified that can be studied in relationship to these disease characteristics. Once the suspected mechanism of action is identified, research can be extended to investigate prevention strategies.

Pancreatic cancer has been chosen as our primary study target. As the fourth leading cause of cancer mortality in the United States, it is relatively common,. The American Cancer Society estimates there will be 37,680 new cases in the United States in 2008.[1] Older age is the strongest predictor of pancreatic cancer risk, with incidence rates increasing from about 10/100,000 per year at age 50 to 80/100,000 per year at age 80. The outcomes of diagnosis are unambiguous, as survival from pancreatic cancer is remarkably poor. Accompanying the 37,680 new cases, there will be 34,290 deaths. It is also fast acting, with median survival being 4 months and 5-year survival less than 5%. It also has associations with modifiable risk factors. For example, current cigarette smokers are 3-5 times more likely to develop pancreatic cancer than those who have never smoked cigarettes. Biomarkers of aging are measurable aspects of physiology that reflect the underlying biological age, which is not necessarily reflected by chronological age.[2] Examples include measures of DNA damage, mitochondrial function, and chromosomal alterations.[2]

A promising biomarker of aging we are studying is telomere length measured in peripheral blood mononuclear cells. Telomeres are the end segments of chromosomes that serve to protect chromosomes from damage during cell division. Telomeres are constructed of hexameric (TTAGGG) DNA repeats bound to proteins.[3–5] A small segment of telomere is lost with each cell division, leading to shortening of the telomere over time and with aging. This telomeric erosion continues through the life of the cell unless telomeres are elongated by the activity of telomerase[6] or other processes. In the absence of elongation, telomeres are eventually exhausted, leading to an inability to bind their proteins, a condition termed telomere crisis. The absence of an intact telomere leads to sticky DNA ends and eventually apoptosis or senescence.[7] In some cases, abnormal cells may escape apoptosis or senescence[8] during telomere crisis and proceed with mitosis resulting in daughter cells with

gross chromosomal abnormalities.[9–12] This phenomenon of cells surviving telomere crisis has been proposed as an important, possibly critical, step in malignant transformation for age-related cancers.[9,13–14]

Telomere attrition and crisis represent a plausible biological mechanism whereby older age may lead to an increase in the risk for pancreatic cancer. Importantly, the rate at which telomeres shorten is variable and is influenced by several external factors that have been identified as risk factors in cancer epidemiology studies: obesity and cigarette smoking,[15] body mass index and insulin resistance,[16] and diabetes.[17–21]

Our group is working to quantify the associations between telomere length and risk for pancreatic cancers and to identify modifiable risk factors that are related to telomere length. This work may help guide future prevention strategies by targeting mechanisms that operate through telomere shortening.

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