Cancer & Aging – a high priority research area for NCI

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The WHI is prime to study cancer and aging

Background

Measures of aging relevant to cancer
Estimated cancer prevalence by age in the US population from 1975 (216 million) to 2040 (380 million)

US Population Age ≥ 65 (millions)

Shift in 2030:
Largest growth in the 80+ age groups

U.S Census Bureau 2010
Rise in cancer incidence by 2030 will be much steeper in older adults.
Hypothesized trajectories of aging in cancer survivors

It is unknown whether the multiple “hits” that cancer diagnosis and treatment represent to biological systems lead to a trajectory parallel to “normal” aging but with weakened reserve (phase shift), or to quicker progression to functional decline (accelerated aging).
Research GAPS in Cancer and Aging

More studies of vulnerable older adults and/or those age ≥ 75 are needed
1) study those with comorbidities, function losses, cognitive decline, and frailty
2) understand how cancer and its treatments interact with underlying vulnerabilities

Geriatric assessment measures needed in oncology research
1) Incorporate validated GA measures
2) Collect endpoints, such as maintenance of functional abilities and quality of life
3) Measure mental health and cognitive changes

Incorporate aging biomarkers in oncology research
1) Aging biomarkers to identify those at risk for cancer treatment side effects
2) Tumor samples to assess whether tumor biology changes with aging

Aging factors contribute to cancer—and cancer may also contribute to aging
All of these measures are available in WHI

**Integrating Geriatrics and Oncology**

Factors other than chronological age that predict morbidity & mortality in older adults

- Functional status
- Comorbid medical conditions
- Cognition
- Nutritional status
- Psychological state
- Social support
- Medications (polypharmacy)

Geriatric Assessment
Approaches to measures of Frailty

The Fried phenotype model is based on five physical indicators-output score from 0-5 - must have assessments

- Exhaustion
- Physical activity
- Weakness
- Walking
- Weight loss

The frailty index of deficit accumulation (many) is calculated from a variety of individual health deficits and includes self-report & psychological - a ratio

- Deficits of Symptoms and signs
- Comorbidities
- Activities of daily living
- Social relations and social support
Rockwood’s approach - well suited for WHI

Frailty Index

Rockwood’s approach from CSHA (Canadian Study on Health and Aging) is based on the concept that deficit accumulation – a combination of symptoms, disease, conditions, and disability – can predict frailty.

- Sum of >70 items used to construct FI
- Includes self rated health, function, cognition, and psychosocial risk factors

Rockwood K. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005
Estimating Cellular Age with DNA Methylation Data

Use of DNA methylation to predict biological age

Several different methods to calculate epigenetic age but all can be done with one assay

Horvath. Genome Biology (2013)-adapted from Binder A.
Estimating Cellular Age with DNA Methylation Data

Difference between methylation-predicted age (DNAmAge) and chronological age (AgeAccel) put forth as an index of disproportionate ‘biological’ aging

<table>
<thead>
<tr>
<th>Individual</th>
<th>AgeAccel</th>
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<tbody>
<tr>
<td>1</td>
<td>-1.50</td>
</tr>
<tr>
<td>2</td>
<td>+1.25</td>
</tr>
<tr>
<td>3</td>
<td>-2.00</td>
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AgeAccel has been found to be associated with all-cause mortality

- A meta-analysis of four large prospective cohorts found a 5-year increase in AgeAccel based on the Hannum epigenetic clock was associated with a 16% (95% CI: 1.08-1.25) increased hazard of mortality

- Associated with a 9% (95% CI: 1.02-1.15) increased hazard of mortality based on the Horvath clock

Frailty Status (Fried Phenotype) and Epigenetic Age Acceleration

- Participants were 791 people aged 70 yrs from the Lothian Birth Cohort 1936
  - Physical frailty status was assessed using the Fried frailty phenotype
  - Frailty is defined by three or more of the following components: weakness, self-reported exhaustion, slow gait speed, unintentional weight loss, and low physical activity
  - Pre-frailty is defined as the presence of one or two of these components

<table>
<thead>
<tr>
<th>Epigenetic age acceleration measures, per year increase</th>
<th>Relative risk ratios (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Pre-frail</td>
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<tr>
<td><strong>Extrinsic epigenetic age acceleration</strong></td>
<td></td>
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<tr>
<td>Adjusted for age and sex</td>
<td>1.02 (1.00, 1.04), ( p = 0.083 )</td>
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<tr>
<td>Multivariable-adjusted(^1)</td>
<td>1.02 (0.99, 1.04), ( p = 0.123 )</td>
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<tr>
<td><strong>Intrinsic epigenetic age acceleration</strong></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.01 (0.99, 1.04), ( p = 0.248 )</td>
</tr>
<tr>
<td>Multivariable-adjusted(^1)</td>
<td>1.01 (0.99, 1.04), ( p = 0.316 )</td>
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</tbody>
</table>

Relative risk ratios (95% confidence intervals) for being physically frail or pre-frail according to epigenetic age acceleration at age 70

\(^1\)Adjusted for age, sex, smoking status, alcohol intake, and number of chronic physical illnesses

Binder A
Cellular Senescence as a marker of aging

Adapted from N. Mitin

McHugh and Gil JCB 2017 217(1):65-77
Senescence

**Senescent Cells**
- Permanent cellular arrest
- Resistant to apoptosis
- Inflammatory phenotype

**Accumulate in Tissues**
- Disrupt homeostasis
- Limit repair
- Limit regeneration

**Compromise Patients**
- Low physiologic reserve
- Adverse events
- Disease progression

Graphic adapted from Muñoz-Espín and Serrano Nat Rev Mol Cell Biol 2014

Adapted from N. Mitin
Senescence Biomarker p16

p16 is a well-established marker and regulator of senescent cells, where it blocks the cell cycle and is required to maintain the senescent phenotype.

Dramatic differences in same-aged mice +/- p16-expressing cells

Adapted from N. Mitin

Baker et. al. Nature 2011 (479)232-6
p16 Expression

In humans, p16 expression levels in T-cells increase exponentially with age and vary significantly among individuals of the same chronological age.
P16 in cancer patients

Two main avenues of research:

1. Effect of chemotherapies on p16, chemotherapy-induced age acceleration - Data to be published soon

2. The ability of p16 measured prior to chemo to risk stratify patients
D3 Creatine as a measure of functional muscle to assess sarcopenia

D3-Creatine (D3-Cr) dilution provides a direct and accurate measure of functional muscle.

It relies on a single spot, fasted urine sample taken 48-96 h after dosing with deuterated creatine pill.
D3 much better than DXA in predicting function

Cawthon et al 2019
Current Grants with aging biomarkers in LILAC - submitted or planned

WHI supplement in response to aging trajectories-epigenetic age.
Caan, Binder- to be submitted May 15

R01, P16 as a marker of how chronic diseases contribute to aging.
Feliciano, Caan- submitted Feb 1

R01, D3 creatine as a measure of sarcopenia among cancer survivors.
Banick, Wactawski-Wende-to be submitted June 1