Canaries in the Coal Mine: What We Can Learn about Aging from Survivors of Childhood Cancer?

A WEBINAR TRIBUTE TO DR. ARTI HURRIA

Kiri K. Ness, P.T., Ph.D., F.A.P.T.A.
Monica Gramatges, M.D., Ph.D.
Cancer & Aging Research Group
Using WebEx and webinar logistics

- All lines will be in listen-only mode
- Make sure icons are selected for them to appear as a drop-down option
- Submit questions at any time during the presentation by typing into the Q&A feature on the right-hand side of the WebEx interface.
  - Select Host and a moderator will ask the questions on your behalf
- Closed captioning available by selecting the Media Viewer Panel on the right-hand side of the screen
- This webinar is being recorded
Canaries in the coal mine: What can we learn about aging in survivors of childhood cancer?

Perspectives on Cancer and Aging: Arti Hurria Memorial Webinar Series

January 14, 2020
Objectives

• Describe frail health in childhood cancer survivors

• Identify specific physiologic targets for intervention in childhood cancer survivors

• Begin to understand the pathobiology of frail health in childhood cancer survivors

• Identify opportunities for prevention of frail health in childhood cancer survivors
Frailty

- Loss of physiological capacity that interferes with normal function
- Most commonly described in older adults
  - can be distinguished from disability and co-morbidity
  - identifies individuals highly vulnerable to adverse health outcomes, often precedes chronic disease onset, and is a predictor of early mortality
Frailty and Exposures

Adapted from Buchner 1992
Frailty and Lifestyle

Not Frail

<table>
<thead>
<tr>
<th>Physiologic Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT FRAIL</td>
</tr>
</tbody>
</table>

Age →

Disease
Chemotherapy
Radiation
Surgeries

Lifestyle choices
Sedentary behavior
Poor diet

Adapted from Buchner 1992
Frailty and Intervention

Physiologic Capacity

Disease
Chemotherapy
Radiation
Surgeries

Lifestyle choices
Sedentary behavior
Poor diet

NOT FRAIL

Adapted from Buchner 1992
Physiologic Frailty As a Sign of Accelerated Aging Among Adult Survivors of Childhood Cancer: A Report From the St. Jude Lifetime Cohort Study


National Cancer Institute U01 CA195547
Fried Frailty Criteria

• Five components of fitness from the Cardiovascular Health Study (65-101 years of age)
  – Muscle wasting
  – Muscle weakness
  – Self-reported exhaustion
  – Slow walking speed
  – Low energy expenditure
• Frail: ≥ 3 components
• Pre-frail: 2 components
Frailty in the St. Jude Lifetime Cohort (SJLIFE)

- N=1922 (50.3% male)
- Mean time since diagnosis: 25.5±7.7 years
- Mean age at diagnosis: 8.2±5.6 years
- 43% leukemia
- 33% with CRT

Frail Pre-frail

<table>
<thead>
<tr>
<th>Percent</th>
<th>SJLIFE age 18-50 (mean 33.6±8.1) years</th>
<th>Cardiovascular Health Study age 65-101 years (Fried, 2001)</th>
<th>Controls age 18-50 years (mean 29.0±7.5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frail</td>
<td>7.9</td>
<td>7.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>22.2</td>
<td>15.0</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Prevalence of Frailty Components

<table>
<thead>
<tr>
<th>Component</th>
<th>SJLIFE</th>
<th>Cardiovascular Health Study</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low energy expenditure</td>
<td>44.9%</td>
<td>22.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Low lean mass</td>
<td>29.2%</td>
<td>6.0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>25.2%</td>
<td>17.0%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Weakness</td>
<td>20.0%</td>
<td>6.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Slow walking</td>
<td>20.0%</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
# Frailty and Mortality

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty</td>
<td>151</td>
<td>4.6%</td>
<td>2.6 (1.5-2.8)</td>
</tr>
<tr>
<td>No Frailty</td>
<td>1771</td>
<td>1.4%</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age and number of chronic medical conditions CTCAEv4.0 grade ≥ 3

Compared to adjusted HR in the Cardiovascular Health Study of 2.24 CI = (1.51-3.33)
Treatment and Relative Risk of Frailty

2.3 2.6 2.1 1.9

Adjusted for current age, age at diagnosis, chest radiation, doses of anthracycline, alkylating agents, glucocorticoids, platinum, vinca-alkaloids and methotrexate, duration of chemotherapy, alcohol intake, and body mass index
Validation of the Phenotype

J Clin Oncol, JCO01901266 2019 Dec 4 [Online ahead of print]

Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study

Samah Hayek, DrPH; Todd M. Gibson, PhD; Wendy M. Leisenring, ScD; Jennifer L. Guida, PhD; Maria Monica Gramatges, MD, PhD; Philip J. Lupo, PhD, MPH; Rebecca M. Howell, PhD; Kevin C. Oeffinger, MD; Smita Bhatia, MD, MPH; Kim Edelstein, PhD; Melissa M. Hudson, MD; Leslie L. Robison, PhD; Paul C. Nathan, MD, MSc; Yutaka Yasui, PhD; Kevin R. Krull, PhD; Gregory T. Armstrong, MD, MSCE; and Kirsten K. Ness, MPH, PhD
Participants

• Participants were 10,899 members of the Childhood Cancer Survivor Study (CCSS) ≥ age 18 years and alive at the end of follow-up.
• Retrospective cohort was funded in 1994
• CCSS includes 5-year survivors diagnosed with cancer prior age 21, between 1970-1999, and their siblings
• 31 contributing centers in North America
• Eight common pediatric cancer types
## Self-Report Definition

Frailty was characterized as ≥ 3 of the following self-reported conditions:

<table>
<thead>
<tr>
<th>Component</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low lean mass</td>
<td>BMI &lt;18.5 kg/m² or unintentional weight loss ≥10 lbs in past year</td>
</tr>
<tr>
<td>Self-reported exhaustion</td>
<td>Score ≤40 on vitality subscale of Short-Form 36</td>
</tr>
<tr>
<td>Low energy expenditure (LEE)</td>
<td>Activity levels captured by NHANES physical activity questionnaire, defined as &lt;383 kcal/wk males, &lt;270 kcal/wk females</td>
</tr>
<tr>
<td>Slow walking speed</td>
<td>Limited &gt;3 months in past 2 years walking one block, walking uphill, or climbing a few flights of stairs.</td>
</tr>
<tr>
<td>Weakness</td>
<td>Weakness or inability to move arms</td>
</tr>
</tbody>
</table>
Age-adjusted Prevalence of Frailty by Sex

Overall
- Survivors: 5.8%
- Siblings: 4.1%

Females
- Survivors: 6.9%
- Siblings: 5.2%

Male
- Survivors: 4.7%
- Siblings: 3.0%

*white boxes show population norms

Eggiman et al. Journal of Gerontology: Medical science 2009
Treatment Exposures and Frailty

Prevalence Rate Ratio (95%CI)

- Cisplatin dose ≥ 600 mg/m²: 1.51
- Cranial radiation dose > 40 Gy: 1.44
- Abdominal radiation dose > 40 Gy: 1.38
- Pelvic radiation dose ≥ 34 Gy: 1.46
- Lung surgery: 1.47
- Amputation: 1.36
Treatment Exposures and Frailty, Adjusted for Grade 3-4 Chronic Conditions & Lifestyle

Prevalence rate ratio (95%CI)

- Cisplatin dose ≥600 mg/m²: 1.51
- Cranial radiation: 1.24
- Abdominal radiation dose >40 Gy: 1.44
- Pelvic radiation dose ≥34 Gy: 1.38
- Lung surgery: 1.46
- Amputation: 1.47

Model includes treatment factors, chronic health conditions and lifestyle factors.
Progression of Frailty in the SJLIFE Cohort

Baseline St. Jude Life Assessment
- Treated at St. Jude Children’s Research Hospital
- 10 year survivor
- 18-45 years of age (median 30)
- 2008-2013

Follow-up Assessment
- 2013-2018

4 - 6 years
Participants

- 0-22 years old at diagnosis (median 7)
- 51.6% male
- 16.1% non-white
- 37.9% leukemia
- 19.5% lymphoma
- 10.9% CNS tumor
- 11.0% sarcoma
- 7.2% Wilms tumor
- 4.4% neuroblastoma
- 3.3% retinoblastoma
- 5.8% other

Eligible (N=1566)
- Active refusal (N=40)
- Passive refusal (N=17)

Participants (N=1509)

Completed assessment (N=1432)

Died prior to assessment (N=77)
Prevalence of Frailty & Components

all $p < 0.001^*$
Prevalence of Frailty & Components

- Low lean mass: 18.5% at baseline, 23.3% at follow-up
- Slow walking speed: 1.5% at baseline, 6.9% at follow-up
- Muscle weakness: 10.9% at baseline, 17.9% at follow-up
- Low energy expenditure: 37.0% at follow-up
- Exhaustion: 23.8% at follow-up

All p < 0.001*
## Risk for Death by Frailty Status

<table>
<thead>
<tr>
<th>Frailty Status</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Frailty</td>
<td>3.53</td>
<td>1.95-6.38</td>
</tr>
<tr>
<td>Age (1-year increments)</td>
<td>1.06</td>
<td>1.03-1.10</td>
</tr>
<tr>
<td>Female</td>
<td>0.64</td>
<td>0.40-1.02</td>
</tr>
<tr>
<td>Non-white race</td>
<td>0.88</td>
<td>0.45-1.73</td>
</tr>
<tr>
<td>Cardiac condition</td>
<td>1.97</td>
<td>1.19-3.26</td>
</tr>
<tr>
<td>Pulmonary condition</td>
<td>2.32</td>
<td>1.38-3.89</td>
</tr>
<tr>
<td>Neurological condition</td>
<td>1.91</td>
<td>1.14-3.22</td>
</tr>
<tr>
<td>Endocrine condition</td>
<td>2.59</td>
<td>1.48-4.54</td>
</tr>
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There were 77 deaths in the cohort, 17.4% among those who were frail and 4.3% among those who were not frail.
Specific Targets for Intervention

Percent impaired

- Survivors exposed to cardiotoxic therapies
- Survivors not exposed to cardiotoxic therapies
- Community Controls

1041 survivors, mean age 35±9 years (666 exposed to anthracyclines±chest radiation), 275 community controls (mean age 34±10 years) participated in CPET and strength testing
After a median follow-up of 4 years, there were 24 survivor deaths, 21 (3.3%) among those with and 3 among those without exercise intolerance (Adjusted HR 3.93 (95% CI 1.09-14.14) comparing those with to those without, exercise intolerance.
Physiologic Impairments Start Early

Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia


National Cancer Institute R01CA129384
Physiologic Impairments Start Early

109 children with newly diagnosed ALL, median age 10 (4-18 years), 65.1% male, 63.3% non-Hispanic white
Proximal Strength in Children with Newly Diagnosed ALL

Proximal muscular strength impaired among 109 children with newly diagnosed ALL (7-10 days after dx) – treated on Total XVI or ALL0932 (median age 10 (range 4-18) years)

<table>
<thead>
<tr>
<th></th>
<th>ALL survivors</th>
<th>Population controls</th>
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<tr>
<td><strong>Quadriceps (Newtons)</strong></td>
<td>201.9 (8.3)</td>
<td>236.1 (5.4)</td>
</tr>
</tbody>
</table>

Proximal muscular strength impaired among 109 children with newly diagnosed ALL (7-10 days after dx) – treated on Total XVI or ALL0932 (median age 10 (range 4-18) years)
Example of Fatty Infiltration of Proximal Muscle

12 year old male during maintenance therapy for T-cell leukemia
Impairments Often Persist

Bone Mineral Density in Children With Acute Lymphoblastic Leukemia

Hiroto Inaba, MD, PhD; Xueyuan Cao, PhD; Alice Q. Han, BA; John C. Panetta, PhD; Kirsten K. Ness, PhD; Monika L. Metzger, MD; Jeffrey E. Rubnitz, MD, PhD; Raul C. Ribeiro, MD; John T. Sandlund, MD; Sima Jebra; MD; Cheng Cheng, PhD; Ching-Hon Pui, MD; Mary V. Relling, PharmD; and Sue C. Kaste, DO
Bone Loss During ALL Therapy

Baseline (N=340, 0.06)

Week 120 (N=296, -1.08)

2 years off therapy (N=232, -0.72)

Lumbar Z-score

Inaba 2018
Lifestyle is Important

Physical Therapy

Dietary Protein Intake and Lean Muscle Mass in Survivors of Childhood Acute Lymphoblastic Leukemia: Report From the St. Jude Lifetime Cohort Study


Physical Therapy, Volume 96, Issue 7, 1 July 2016, Pages 1029–1038

National Cancer Institute R01 CA132901
Lean Muscle Mass in ALL Survivors

<table>
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<tr>
<th></th>
<th>Percent</th>
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<tr>
<td>Protein intake (g/kg)</td>
<td>7.89%</td>
<td>-0.21%</td>
<td>-9.09%</td>
<td>0.01%</td>
<td>2.38%</td>
<td>-2.43%</td>
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<tr>
<td>Age (years)</td>
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<td></td>
<td></td>
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<tr>
<td>Female sex</td>
<td></td>
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<tr>
<td>Physical activity (METmin/wk)</td>
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<tr>
<td>Resistance training</td>
<td></td>
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<tr>
<td>Cancer survivor</td>
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Conclusions

• Childhood cancer survivors demonstrate an aging phenotype.
• Specific targets for intervention exist.
• Mechanistic studies may reveal new targets for intervention.
• In the meantime, interventions are underway across the childhood cancer survivor continuum.
Next Steps

• Continue investigations to better understand the pathobiology of this aging phenotype.

• Evaluate the contributions of lifestyle to the pathobiology of aging.

• Design and test interventions to address multiple components of the aging phenotype.

• Design dissemination mechanisms for studies with positive results.
Biological indicators and molecular mechanisms of premature, accelerated aging in survivors of childhood cancer

M. Monica Gramatges, MD, PhD
Associate Professor of Pediatrics
Texas Children’s Cancer and Hematology Centers, Dan L. Duncan Comprehensive Cancer Center
Baylor College of Medicine
January 14, 2020
Objectives

- Review hallmarks of physiologic aging
- Review the current understanding of molecular mechanisms underlying premature aging in survivor populations
- Discuss the potential impact of chemotherapy and radiation on general and organ-specific aging
- Suggest opportunities for therapeutic intervention
- Provide considerations for proposals-in-development that include aims investigating aging-related biomarkers
Risks for late effects are determined by treatment exposure and dose, and further influenced by demographics, behavioral and lifestyle choices, and genetic factors.

Children’s Oncology Group Long Term Follow Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, v.5.0
http://www.survivorshipguidelines.org//default.htm
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Chronic health conditions resulting from the accumulation of late effects over time, excess risk of frailty, and limitations in physical performance, together suggest that childhood cancer diagnosis and treatment augment risk for premature, accelerated aging in survivors.
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Survivor risk for **chronic health conditions** exceeds that of age-comparable controls

Risk for new onset chronic conditions in Childhood Cancer Survivor Study participants

Cupit-Link et al., *ESMO Open*, 2017

Armstrong et al., *J of Clinical Oncology*, 2014
One third of survivors develop a severe, disabling, or life threatening chronic health condition within 20 years of completing therapy.

Graph modified from Gibson et al., *Lancet Oncol*, 2018.
Survivors experience **limitations in physical performance**, such as decreased grip strength and slower walk speed, compared with age-similar controls.

Handgrip strength, brain tumor survivors and an age- and sex-matched comparison group.

Six-minute walk distance, ALL survivors

Henderson et al., *ASCO Educational Book*, 2014
Survivors are more likely to be **pre-frail and frail** than age-comparable controls, approaching the frequency observed in individuals who are decades older.
Are the molecular mechanisms underlying physiologic aging similar to those experienced by survivors with signs of premature, accelerated aging?
Physiologic aging is characterized by a spectrum of hallmarks associated with age-related pathology

Lopez-Otin et al., Cell, 2013
Physiologic aging is characterized by a spectrum of hallmarks associated with age-related pathology.

Primary hallmarks
Causes of damage

Antagonistic hallmarks
Responses to damage

Integrative hallmarks
Culprits of the phenotype

Lopez-Otin et al., Cell, 2013
Primary hallmarks of physiologic aging: **Genomic instability**

- Somatic mutations, chromosomal aneuploidies, and copy number variation increase with physiologic aging
  - $10^4$–$10^5$ DNA lesions are generated each day, arising from intrinsic (e.g. reactive oxygen species) and extrinsic sources (e.g. UV or ionizing radiation, chemotherapy)
  - Clonal hematopoiesis predicts all-cause mortality and risk of hematologic cancer
- DNA repair mechanisms resolve specific types of DNA damage (e.g. DNA mismatch repair, base-excision repair, non-homologous end joining, homologous recombination), but capacity for repair declines with increasing age
- Aging-related clinical outcomes associated with genomic instability
  - Cancer
  - Neurological disease
  - Osteoarthritis
  - Mitochondrial dysfunction, cellular senescence, and stem cell exhaustion
Evidence of **genomic instability** in survivors of childhood cancer

- Neuroblastoma survivors are at increased risk for second malignancies: A Report from the International Neuroblastoma Risk group Project, *Eur J Cancer*, 2017
  - Variants implicating DNA repair genes associated with SMN
- *XRCC1* and glutathione-S-transferase gene polymorphisms and susceptibility to radiotherapy-related malignancies in survivors of Hodgkin disease, *Cancer*, 2004

Wang et al., *J Clin Oncol*, 2017
Primary hallmarks of physiologic aging: **Telomere attrition**

- Telomeres = DNA-protein structures at chromosome ends
  - Shorten with DNA replication and with chronologic aging
  - Loss of telomeric DNA with each cell division leads to replicative senescence or apoptosis (Hayflick limit)
- Aging-related clinical outcomes associated with excess telomere attrition
  - *Cancer*
  - *Pulmonary disease*
  - *Atherosclerosis and coronary heart disease*
  - *Osteoarthritis*
  - *All-cause mortality*
  - *Poor grip strength*
  - *Sarcopenia*
  - *Cellular senescence and stem cell exhaustion*

Ness et al., *JCO*, 2018

Njajou et al., *PNAS*, 2007
Evidence of **telomere attrition** in survivors of childhood cancer

- Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging, *Cancer*, 2017
  - Survivors had significantly shorter TL compared with controls, especially survivors who received cranial RT
- Clinical and biological markers of premature aging after autologous SCT in childhood cancer, *Bone Marrow Transplant*, 2017
  - Neuroblastoma survivors had significantly TL compared with age- and sex-matched controls
Evidence of **telomere attrition** in survivors of childhood cancer

Telomere attrition with age in the SJLIFE cohort compared with controls

Mean LTL in SJLIFE is significantly shorter overall and across all diagnosis groups when compared to controls with no prior history of cancer

\[ y = 0.0515x + 7.8941 \]
\[ R^2 = 0.1738 \]

*Drs. Ness, unpublished data*
Evidence of **telomere attrition** in survivors of childhood cancer

Telomere shortening in leukocyte subsets among survivors enrolled to the Childhood Cancer Survivor Study with and without second cancers

LTL in CCSS survivors deviates below the population mean, with a higher than expected frequency of TL in the <1st percentile

*Drs. Gramatges, unpublished data*
Primary hallmarks of physiologic aging: **Epigenetic alteration**

- DNA methylation (DNAm) adds methyl groups to the 5’ cytosine of C-G dinucleotides (CpGs)
- Epigenetic modification, e.g. global demethylation and increase in site-specific variability in DNAm, occurs with aging
- Epigenetic clock: preferential hypermethylation of CpG island loci correlating with chronological age
  - **Age acceleration residual** = difference between DNAm age and chronological age
- Aging-related clinical outcomes associated with increased age acceleration residuals
  - Frailty
  - Poor grip strength, sarcopenia
  - Cancer
  - Type II diabetes, neurological disease

Horvath et al., *Nat Rev Genet*, 2018
Evidence of **epigenetic alteration** in survivors of childhood cancer

- DNA methylation patterns of adult survivors of adolescent/young adult Hodgkin lymphoma compared to their unaffected monozygotic twin, *Leuk Lymphoma*, 2019
  - Excess epigenetic aging (blood DNAm age) in survivors

  - BMI-DNAm loci associated with obesity in ALL survivors treated without CRT

- T cell epigenetic remodeling and accelerated epigenetic aging are linked to long-term immune alterations in childhood cancer survivors, *Clín Epigenetics*, 2018
  - Accelerated epigenetic aging in T cells associated with chronic inflammatory disease in survivors

- DNA methylation of a novel PAK4 locus influences ototoxicity susceptibility following cisplatin and radiation therapy for pediatric embryonal tumors, *Neuro Oncology*, 2017
  - A CpG methylation loci (cg14010619) is associated with ototoxicity severity
Evidence of epigenetic alteration in survivors of childhood cancer

In the SJLIFE cohort, the age acceleration residual was increased among survivors exposed to chest or abdominal RT vs. survivors not exposed to RT, suggesting RT contributes to accelerated epigenetic aging. The age acceleration residual was also associated with TL (adjusted model), explaining 4% of variance in TL.

In CCSS, ALL survivors (n=96) DNAm age exceeds chronologic age by 17.8 years (p < 0.0001). Age at diagnosis was inversely correlated with age acceleration residual (p=0.001), suggesting younger subjects are more susceptible to accelerated epigenetic aging.

Drs. Ness, Lupo, and Gramatges, unpublished data
Primary hallmarks of physiologic aging: **Loss of proteostasis**

- Proteolytic pathways responsible for unfolded protein quality control become hypofunctional with aging
  - Autophagy–lysosomal system
  - Ubiquitin-proteasome system
- Aging-related clinical outcomes associated with impaired/dysregulated proteostasis
  - Alzheimer’s disease
  - Parkinson’s disease
  - Cataracts
  - Pulmonary disease

Kaushik et al., *Nat Med*, 2015
Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer: **Inflammation**

- Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging, *Cancer*, 2017
  - Plasma levels of IL-2, IL-10, IL-17A, and CRP significantly higher vs. healthy controls
- Clinical and biological markers of premature aging after autologous SCT in childhood cancer, *Bone Marrow Transplant*, 2017
  - Higher levels of CRP among survivors than controls
- Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia, *Cancer*, 2017
  - Worse executive function, processing speed, and behavioral symptoms in female survivors with higher levels of IL-6, IL-1β, and CRP
- Elevated markers of inflammation and endothelial activation and increased monocyte counts in adult survivors of childhood ALL, *Immunobiology*, 2013
  - Chronic inflammatory activation and immune dysregulation in adult survivors
Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer – **oxidative stress and mitochondrial dysfunction**

  - Inferior cognitive or behavioral outcomes associated with SNPs in genes related to oxidative stress and/or neuroinflammation

  - Markers of oxidative stress (oxidation protein products, oxidized low-density lipoprotein), inflammation (CRP) and endothelial dysfunction (E-selectin, PAI-1) higher in HL survivors
Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer – **mitochondrial dysfunction**

In the SJLIFE cohort, mitochondrial copy number declines with age at a faster rate than expected among childhood cancer survivors, with a loss of 9 copies per ten years compared to an expected loss of 1.5 copies per 10 years.

*Drs. Ness, unpublished data*
Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer: Cellular senescence

• Muscle weakness, frailty, metabolic and cardiovascular dysfunction, risk for second cancers, and pulmonary fibrosis, conditions common to survivors, have been associated with cellular senescence in non-survivor populations

• Expression of the senescence marker p16INK4a in skin biopsies of acute lymphoblastic leukemia survivors: a pilot study, Radiat Oncol, 2013
  • p16INK4a mRNA levels were 5.8 times higher in scalp skin biopsies (targeted by cranial RT) compared to buttocks skin biopsies
### Potential interventions targeting mechanisms of aging

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effects</th>
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<tr>
<td>Deubiquitylase inhibitors and proteasome activators</td>
<td>Clearance of harmful protein in human cells</td>
</tr>
<tr>
<td>Metformin</td>
<td>Activation of telomerase expression, reduction of reactive oxygen species, decreased IGF signaling</td>
</tr>
<tr>
<td>Exercise</td>
<td>Reduce chronic inflammation, mitigate age-related telomere attrition, alteration of DNA methylation patterns</td>
</tr>
<tr>
<td>Caloric restriction/intermittent fasting</td>
<td>Decreased IGF signaling, mTOR inhibition, sirtuin activation, autophagy activation</td>
</tr>
<tr>
<td>Resveratrol and polyphenols</td>
<td>Upregulation of SIRT1 activity, promotion of autophagy</td>
</tr>
<tr>
<td>Senolytics (e.g. bcl-2 inhibitors)</td>
<td>Induction of apoptosis via disabling of anti-apoptotic pathways in senescent cells. Improves metabolic dysfunction, osteoporosis, frailty, muscle wasting</td>
</tr>
<tr>
<td>mTOR inhibitors (e.g. rapamycin)</td>
<td>Delays aging phenotype, promotes protein autophagy, extends lifespan</td>
</tr>
<tr>
<td>Danazol</td>
<td>Telomere maintenance/lengthening</td>
</tr>
</tbody>
</table>
Conclusions...
Insults to molecular integrity and physiologic capacity provoked by exposure to chemotherapy and/or radiation may be associated with an excess risk and advanced onset of age-related diseases and frailty in survivors of childhood cancer.

Ness et al., *J of Clin Oncol*, 2018
Physiologic aging is a complex, multifactorial process influenced by genetic, epigenetic, and environmental factors.

The phenotypic differences between physiologic aging and the early aging experienced by survivors are not yet clear, nor are distinctions in the molecular mechanisms that drive these phenotypes.

Franceschi et al., *Frontiers in Medicine*, 2018
Physiologic aging is characterized by disparities in functional decline between organ systems, suggestive of inherent variation in tissue susceptibility to chronologic aging.

Among survivors, chemotherapy and radiation may differentially impact specific organ systems, leading to organ-specific accelerated aging that is dependent on the cumulative effect of treatment exposures.

Khan et al., *Aging Cell*, 2017
Final thoughts regarding grant development: *considerations and lessons learned*

- **Rigor of prior research**
  - Is there evidence for association with aging-related outcomes in cancer survivor populations?
  - Preliminary data?

- **Consider molecular mechanisms associated with organ-specific outcomes**
  - e.g. markers of oxidative stress in studies investigating cardiotoxicity in survivors

- **Provide rationale for limiting investigation to a subset of biomarkers**

- **Acknowledge and anticipate potential differences between physiologic aging and survivor aging, for both the phenotype and the underlying molecular mechanisms**

- **Consider the relationship of the outcome with longitudinal changes in biomarkers over time, if possible**

- **Cost, feasibility, power**
Q&A
Future webinars

April 9, 2020, 12-1 p.m. ET
• Luigi Ferrucci and Morgan Levine

Send speaker suggestions and other feedback to:
NCIDCCPSagingwebinar@mail.nih.gov