The Relationship Between Aging, Cognition, and Cancer

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Introduction

- Demographics of Aging
  - Cancer
  - Cognitive Function

- Conceptual Model of Aging, Cancer, & Cognition

- Cognitive Studies: Older Adults with Cancer

- Potential Interventions
US Population Age $\geq 65$ (millions)

Year

U.S Census Bureau
Life Expectancy is Increasing

[Bar chart showing life expectancy by age and gender from 1900, 2000, and 2050.]

Year

Age

National Vital Statistics Report
Implications of an Aging Society

- Increase in the number of cases of cancer
- Increase in the number of cases of dementia
Projected Rise in Cancer Incidence from 2010 to 2030

- 67% in patients 65+
- 11% in patients <65

Smith et al, J Clin Oncol, 2009
Most Survivors are Older Adults

65 yrs or Older  
60%

< 65 yrs  
40%

Of 10.8 million cancer survivors, an estimated 6.8 million are 65 years or older

Rowland, Semin Oncol Nurs 2008
Worldwide Statistics: Cases of Dementia

Millions

2010  2030  2050

Dementia in Older Adults

World Alzheimer Report 2010
Economic Impact of Dementia

- 0.5% of the world’s population live with dementia
- Worldwide cost of dementia:
  - $604 billion US dollars in 2010
- If dementia care were a country, it would be the world’s 18th largest economy
- By 2030:
  - 85% increase in costs worldwide due to dementia

*World Alzheimer Report 2010*
The Population is Aging

The Number of Older Adults With Cancer is on the Rise

Increase in Number of Cancer Cases and Number of Patients with Dementia

What is the Link Between Aging, Cancer, & Cognition?
Age, Cancer, and Cognition

Aging

Cancer &
Cancer Therapy

Cell Senescence
Inflammation
DNA Damage
Oxidative Stress
↓ in Telomere Length

Cognition
Does cancer therapy accelerate…
Physiologic aging?      Cognitive aging?

Will I recover?
I would rather die than take a treatment that causes:

- functional impairment: 74%
- cognitive impairment: 88%

Fried et al. NEJM 2002: 346 (14): 1061
The Older Patient: Gaps in Knowledge

- How does cancer therapy impact physiologic aging?
- How does cancer therapy impact cognitive aging?
- Does this impact vary depending on patients’...
  - Age at treatment?
  - Comorbid conditions?
  - Overall health status?
Potential Trajectories of Cognitive Function

- No Cancer
- Cancer survivor

**Phase Shift Hypothesis:**
The trajectory of cognitive dysfunction parallels normal aging.

**Accelerated Aging Hypothesis:**
The trajectory of cognitive dysfunction is accelerated in comparison to normal aging.

*Hurria & Ahles 2012*
Cancer Therapy, Cognition, & Aging

Summary of the Evidence

- SEER Studies
- Twin Studies
- Prospective/Longitudinal Studies
  - Short-Term Impact
  - Long-Term Impact
- Survivorship Studies
Chemotherapy & Risk of Dementia

- Risk of dementia in breast cancer survivors who were exposed and were not exposed to chemotherapy
- SEER data linked to Medicare Claims data
- Results:
  - Chemotherapy not associated with ↑ risk of dementia over time for any age group  
    \[\text{Baxter et al. JAGS 2009}\]
  - Chemotherapy may be associated with long-term cognitive changes  
    \[\text{Heck et al. JAGS 2008}\]

Further studies are needed with formal neuropsychological assessments.
Cancer as Risk Factor for Long-Term Cognitive Deficits and Dementia

- Co-twin control study using the Swedish Twin Registry
- 702 cancer survivors age $\geq 65$ compared to their cancer-free twins

Methods:

- Telephone Cognitive Screening
- Blessed Dementia Rating Scale
- Complete workup by a neurologist and psychologist for twin pairs if one individual scored a 3 during screening
- Dementia workup identified 486 twin pairs discordant for cancer

Heflin et al, JNCI, 2005
Prevalence of Cognitive Dysfunction in Twins Diagnosed With and Without Cancer

Heflin et al., JNCI, 2005
Cognitive Impairment Higher in Female Cancer Survivors

Impact of Age and Cognitive Reserve on Cognitive Function

- Patients with breast cancer (chemotherapy vs. no chemotherapy) and healthy controls
- Battery of neuropsychological & psychological tests
- Timepoints:

  Before Treatment 1 month 6 months 18 months Post-treatment

Ahles et al, J Clin Oncol, 2010
Increased Age and Lower Cognitive Reserve Associated with Decline in Processing Speed

Ahles et al, J Clin Oncol, 2010
Age and baseline cognitive reserve are predictors of post-treatment cognitive function in the Processing Speed domain.

*Ahles et al, J Clin Oncol, 2010*
Cognitive Function in Breast Cancer Survivors 10 Years After Chemotherapy

- Breast cancer survivors age $\geq 65$ (N=30)
  - Received treatment during midlife (CMF or anthracycline)
- Healthy controls, matched on age, education, and IQ (N=3)
- 3 hour standardized neuropsychological battery
- One timepoint

- Cancer survivors scored significantly lower in cognitive domains related to the frontal-subcortical brain regions
- Cancer survivors exposed to chemotherapy may be at risk of accelerated cognitive dysfunction associated with age-related brain changes

Yamada et al, JNCN, 2010
Cognitive Function in Breast Cancer Survivors 20 Years After Chemotherapy

- Case-Cohort Study
- Breast cancer survivors who received adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF)
- Healthy controls
- Battery of 7 neuropsychological & psychological tests
- One timepoint

Survivors of breast cancer exposed to chemotherapy performed similar or worse when compared to the healthy control group

*Koppelmans et al, J Clin Oncol, 2011*
Chemotherapy and Cognitive Function

Decreased:
- Verbal Memory
- Processing Speed
- Executive Function
- Psychomotor Speed

Koppelmans et al, J Clin Oncol, 2011
The Patient’s Perspective: Adjuvant Breast Cancer Therapy and Cognitive Function

- Longitudinal Prospective Study
- 45 patients ≥ age 65 with stage I to III breast cancer
- Questionnaire performed prior to chemotherapy and 6 months post chemotherapy
  - Squire Memory Self Rating Questionnaire
  - Patient’s perception of:
    - New learning
    - Working memory
    - Remote memory

*Hurria et al. Breast Cancer Research, 2006*
Percent of Patients Perceiving Memory Decline 6 Months after Chemotherapy

Perceived memory decline was most pronounced in patients with below average memory at baseline

_Hurria et al. Breast Cancer Research, 2006_
Longitudinal Cognitive Function of Older Women Receiving Adjuvant Chemotherapy

- 28 patients with stage I-III breast cancer
- Mean age 71 (range 65-84)
- Neuropsychological and functional testing performed:
  - Pre-chemotherapy
  - 6 months post-chemotherapy

*Hurria et al. JAGS, 2006*
Definition of Cognitive Decline

1 SD decline in $\geq 2$ neuropsychological domains

Hurria et al. JAGS, 2006
Conclusions

- 64% of older patients perceived that they had preexisting memory problems prior to beginning chemotherapy, and this cohort was most likely to perceive worsening memory after chemotherapy.

- Approximately 50% perceived a worsening of memory from pre-chemotherapy to 6 months post-chemotherapy.

- The memory domain that patients perceived as most likely to be affected was the ability to acquire new information.

- 25% with a 1SD decline in 2 or more domains.
Aging begins from the minute we are born.
The Present Conceptual Model:
Factors Impacting Cognition in Cancer Patients

Janelsins et al, Semin Oncol, 2011
Are We Missing Key Factors That Impact Cognitive Function?

- **Cancer Diagnosis & Cancer Therapeutics**
  - Genetic Variation
    - APOE
    - ACE Genotype
    - UBQLN1 Gene
  - Comorbidity
    - Vascular Risk Factors
    - Cardiovascular disease
    - Obesity
    - Chronic Kidney disease

- **Aging**
  - Psychological State
    - Anxiety
    - Depression
    - Fatigue

- **Patient’s Cognition**
  - Sociodemographics
    - Gender
    - Race/ethnicity
    - Education
  - Lifestyle
    - Physical activity
    - Diet/Nutrition
    - Smoking
    - Alcohol
The Aging Brain

- ↓ in cerebral blood flow
- Neuronal Loss ↑ – White matter atrophy
- Impairments in:
  - Processing speed
  - ↑ in reaction time
  - Sequence-learning ability
  - Short-term memory

Sehl et al. The Cancer Journal 2005
Brain Atrophy in Healthy Aging

- Cross-section MRI study

- 142 healthy elderly patients (age 60-91) vs. 122 patients with mild to moderate Alzheimer’s disease

↓ in volume of the cerebral cortex and subcortical brain structures were seen in healthy participants after 1 year

Fjell et al. J Neurosci 2009
Are We Missing Key Factors That Impact Cognitive Function?

- Genetic Variation
  - APOE
  - ACE Genotype
  - UBQLN1 Gene

- Lifestyle
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- Comorbidity
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- Cancer Diagnosis & Cancer Therapeutics

- Aging

- Psychological State
  - Anxiety
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  - Fatigue

- Sociodemographics
  - Gender
  - Race/ethnicity
  - Education
Comorbidity Increases with Age

Number of Comorbidity

Yancik et al, Cancer 1997
Most Common Comorbid Illnesses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>42.9</td>
</tr>
<tr>
<td>Heart-related conditions</td>
<td>39.1</td>
</tr>
<tr>
<td>Arthritis</td>
<td>34.9</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>31</td>
</tr>
<tr>
<td>Anemia</td>
<td>22.6</td>
</tr>
<tr>
<td>Eye Problems</td>
<td>19</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>18</td>
</tr>
<tr>
<td>Previous cancer</td>
<td>15.4</td>
</tr>
<tr>
<td>COPD</td>
<td>14.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Yancik et al, Cancer 1997
Risk of Dementia Associated with Cardiovascular Risk Factors

- 111,151 pts in the Atherosclerosis Risk in Communities study
- Underwent a physical exam and cognitive testing

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.6 (95% CI, 1.2-2.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2 (95% CI, 1.6-3.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.7 (95% CI, 1.2-2.5)</td>
</tr>
</tbody>
</table>

Hypertension, diabetes and smoking in midlife → ↑ risk of being hospitalized with dementia later in life

Alonso et al, J Neurol Neurosurg Psychiatry 2009
Diabetes Associated with Risk of Dementia

- Systematic review evaluating incidence of dementia in people with diabetes mellitus
- 14 longitudinal population-based studies
- Results:
  - Incidence of dementia higher among individuals with diabetes vs. without diabetes (7 out of 10 studies)
  - Diabetes was associated with high risk of Alzheimer’s disease (8 out of 13 studies)
  - Diabetes was associated with high risk of vascular dementia (6 out of 9 studies)

Biessels et al, Lancet Neurol 2006
Renal Impairment is Associated with Risk of Incident Dementia

- Cardiovascular Health Cognition Study
- 3349 participants without prevalent dementia
- Median 6 year follow-up
- Results:
  - Moderate renal insufficiency → 37% ↑ risk of dementia
  - Higher serum creatinine was associated with vascular dementia, not Alzheimer disease

Seliger et al, J Am Soc Nephrol 2004
Obesity and Risk of Dementia

- Cardiovascular Health Study
- 2798 adults without dementia (mean age: 74.7 years)
- Median 5.4 year follow-up

Results:

- 480 individuals developed dementia
- Obesity (BMI > 30) and cardiovascular risk factors mid-life → ↑ risk of dementia in late-life

Fitzpatrick et al, Arch Neurol. 2009
↑ Risk of dementia with ↑ in BMI at age ≥ 65

Fitzpatrick et al, Arch Neurol. 2009
Are We Missing Key Factors That Impact Cognitive Function?

**Cancer Diagnosis & Cancer Therapeutics**

- Genetic Variation
  - APOE
  - ACE Genotype
  - UBQLN1 Gene

**Aging**

- Psychological State
  - Anxiety
  - Depression
  - Fatigue

**Patient’s Cognition**

- Comorbidity
  - Vascular Risk Factors
  - Cardiovascular disease
  - Obesity
  - Chronic Kidney disease

- Sociodemographics
  - Gender
  - Race/ethnicity
  - Education

**Lifestyle**

- Physical activity
- Diet/Nutrition
- Smoking
- Alcohol
To Understand the Association Between Cancer/Cancer Therapy & Cognitive Function

Should we study an older adult population?

Or is it just too complex?
Embracing the Complexities: Rationale to Study Older Adults

- Important part of the informed consent process: Patients state it will influence their decision making

- Impact of cognitive decline
  - Decline in functional status
  - Ability to live independently
  - Overall survival

- Cognitive frailty
  - Are patients with baseline cognitive problems more vulnerable to cognitive side effects?
Understanding Frailty

Population: Community dwelling adults age 65 and older

- Cardiovascular Health Study
- 5317 participants
- Age 65 years or older
- Baseline, 4 yrs & 7 yrs of follow-up

Identified Factors Associated with:
- Falls
- Hospitalizations
- Decline in ADLs
- Decline in Mobility
- Death

A Phenotype of Frailty

Factors Defining Frailty:

- Weight loss
- Weakness
- Poor energy/endurance
- Slowness
- Low physical activity


- 0 factors: Not frail
- 1 or 2 factors: Intermediate
- 3 or more factors: Frail
Phenotype of Frailty Predictive of 5 Adverse Outcomes

Frailty Independent Predictor of:
- Death
- Hospitalization
- Falls
- ADL Disability
- Decrease Mobility

Incidence of Adverse Outcomes Associated with Frailty

Pathway to Frailty

**Molecular and Disease**
- Oxidative stress
- Mitochondrial deletions
- Shortened Telomeres
- DNA damage
- Cell senescence
- Gene variation
- Inflammatory Diseases

**Impaired Physiological**
- Inflammation
  - Interleukin-6
- Neuroendocrine Dysregulation
  - Insulin–like growth factor-1
  - Dehydroepiandrosterone Sulfate
  - Sex steroids
- Anorexia
- Sarcopenia, Osteopenia
  - Immune function
  - Cognition
  - Clotting
  - Glucose Metabolism

**Clinical**
- Slowness
- Weakness
- Weight Loss
- Low Activity
- Fatigue

How does cancer treatment influence the pathway to frailty?

*Walston et al., JAGS 2006*
Increased # of Physiologic Abnormalities → Increased Risk of Frailty

Fried, LP et al., J Gerontol A Bio Sci Med Sci
Is there a Link Between Physical Function and Cognition?

- Ginkgo Evaluation of Memory Cross-Sectional Study
- 3035 healthy participants – Mean age 78.6 yrs
- Measures evaluated:
  - Gait speed (walking 15 ft)
  - Activities of Daily Living
  - Modified Mini Mental State Examination
- Results:
  - Low cognitive function was 2x greater in participants who were in the slowest quartile for walking speed

Performance-based measures and functional reserve tasks are better predictors of early cognitive decline

*Fitzpatrick et al, Journal of Gerontology 2007*
Gaps in Knowledge?

Definition of cognitive frailty

How is physical frailty associated with cognitive frailty?

Should cognitive function be included as a part of the frailty index?
Interventions
What Can We Modify Now?

Cancer Diagnosis & Cancer Therapeutics
- Genetic Variation
  - APOE
  - ACE Genotype
  - UBQLN1 Gene
- Psychological State
  - Anxiety
  - Depression
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- Comorbidity
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Patient’s Cognition
## Physical Activity and Cognitive Aging

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Groups</th>
<th>Time</th>
<th>Outcome: Improvement In…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker 2010</td>
<td>Aerobic Exercise</td>
<td>6 mo.</td>
<td>Executive Function</td>
</tr>
<tr>
<td>Anderson-Hanley 2010</td>
<td>Chair &amp; Standing + Weights</td>
<td>4 wks</td>
<td>Working memory &amp; Executive Function</td>
</tr>
<tr>
<td>Lautenschlager 2008</td>
<td>Walking</td>
<td>6 mo.</td>
<td>Delayed Recall</td>
</tr>
<tr>
<td>Van Ufflelen 2008</td>
<td>Walking</td>
<td>1 yr</td>
<td>Memory &amp; Executive Function</td>
</tr>
<tr>
<td>Erickson 2011</td>
<td>Stretching/Toning</td>
<td>1 yr</td>
<td>Hippocampal volume ↑</td>
</tr>
</tbody>
</table>

**Do you want to go for a run now?**

*Jak, Curr Topics Behav Neurosci 2011*
It Is Never Too Late

100 Year Old Completes Marathon
Cognitive Impairment due to Chemotherapy Ameliorated by Physical Activity

- Laboratory Animal Study done in 60 male hooded Wistar rats

- Study Schema:
  - Treated with 5-Fluorouracil, Oxaliplatin, or both
  - No Chemotherapy

- Results:
  - Combination therapy significantly impacted cognition
  - Exercising post-chemotherapy improved cognition compared to the sedentary group

Fardell et al, Psychopharmacology 2012
Effects of Memory Training

- Randomized Controlled Trial
- 8-week cognitive training regimen (N=22) vs. Control participants who did not receive any intervention (N=20)
- MRI scan and Memory testing at baseline and post 8 weeks
- Results:

Engvig et al, Neuroimage 2010

Memory training improved source memory & ↑ cortical thickness
Strategic Research Priorities from the NIA

- Understand the mechanisms involved in:
  - Brain’s normal aging
  - Role of cognition in everyday functioning
  - Protective factors for cognitive function
  - Pathogenesis neurodegenerative disorders of aging.

- Develop better ways to identify people with normal brain aging vs. development of cognitive impairment

- Translate biological mechanisms related to cognitive function and age into strategies for diagnosis, treatment, and/or prevention

- Conduct research to better understand and develop interventions to address the caregiving needs for patients with cognitive disorders
Conclusions

- Our society is aging
- There will be an increase in:
  - the number of cases of cancer
  - the number of cases of dementia
- The majority of cancer survivors are older adults
- Understanding the association between aging, cancer (and therapy), and cognitive function is critical
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Geriatrics

Geriatric Oncology

Oncology
The True Body-Mind Connection

After thirty, a body has a mind of its own.
- Bette Midler