

**CANCER-RELATED
COGNITIVE IMPAIRMENT:
MORE THAN A SIDE EFFECT OF
CHEMOTHERAPY**

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OUTLINE

- Background
- Causes and underlying mechanisms
- Study regarding association with physical function
- Screening and diagnosis
- Treatment

LEARNING OBJECTIVES

1. Identify causes for cancer-related cognitive impairment (CRCI)
2. Discuss morbidity associated with CRCI
3. Describe evidence-based interventions for CRCI

HISTORICAL PERSPECTIVE

- Awareness since 1970s - "Serial Cognitive Testing in Cancer Patients Receiving Chemotherapy" (Oxman 1980)
- "Chemobrain" defined in late 1990s in cross-sectional studies in breast CA
- 2002 – Ahles et al. showed long-term effects of chemo
- 2004 – Wefel et al. first prospective longitudinal study
- Growing appreciation for cognitive difficulties resulting from cancer **and** its treatments over the last 15-20 years (i.e. CRCI, CRCD)

QUALITY OF COGNITIVE PROBLEMS REPORTED POST-TREATMENT

- Memory
- Concentration
- Executive function
- Ability to learn new material
- Subtle or dramatic
- Variable course

PREVALENCE OF CRCI

- Up to 30% with cognitive impairment before chemotherapy
- 75% report cognitive deficits during treatment
- 15-50% exhibit objective impairment after chemotherapy
- Lasts years after treatment

Janelins 2011, Wefel 2006

SIGNIFICANCE OF CRCI

- Associations
 - adverse mental health
 - inability to return to work
 - double the risk of dementia
 - worse HRQOL
 - increased mortality
- Greater influence on chemotherapy prescribing than age or functional status
- One of the most feared problems among cancer survivors

Janelins 2011, Wefel 2006, Vardy & Tannock 2007, Hsieh 2018, Mohile 2018

NEUROPLASTICITY

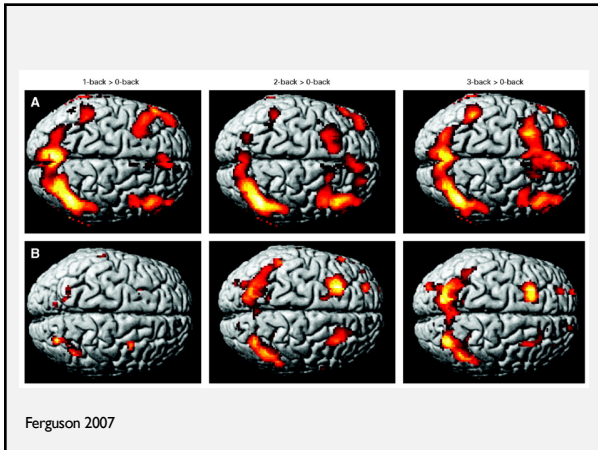
- Brain's ability to reorganize itself to repair, compensate, adapt and learn new things
- Most natural brain recovery occurs in the first 1-2 yr after diagnosis and treatment
- Some return to "normal" function, others with persistent deficits, and some develop new problems not seen earlier in treatment

Correa 2008 and Wefel 2010

MECHANISMS

- Direct toxicity
- Cytokine-mediated neuroinflammation
- Oxidative stress
- Genetic
 - Survivors w/ APOE4 with worse cognitive problems
 - Breast CA survivors treated w/ chemotherapy with COMTVal158Met had greater decline
 - BDNF Met/Met genotype protective against chemo-induced cognitive changes
 - Neuronal plasticity genes, DNA damage and repair genes, mediate inflammation

Ahles 2003, Mandelblatt 2018, Small 2011, Ng 2016



IMAGING FINDINGS

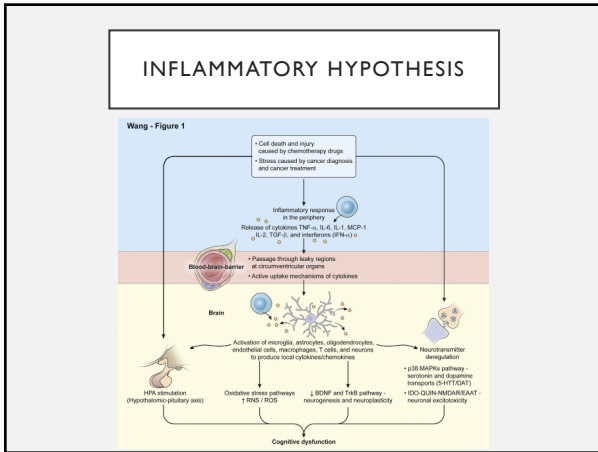
- ↓gray matter volume
- ↓white matter connectivity
- Altered functional brain activation and connectivity
- Decreased volume and connectivity correlate with worse function

McDonald 2010, DePaez 2012, Saykin 2003, Inagaki 2007

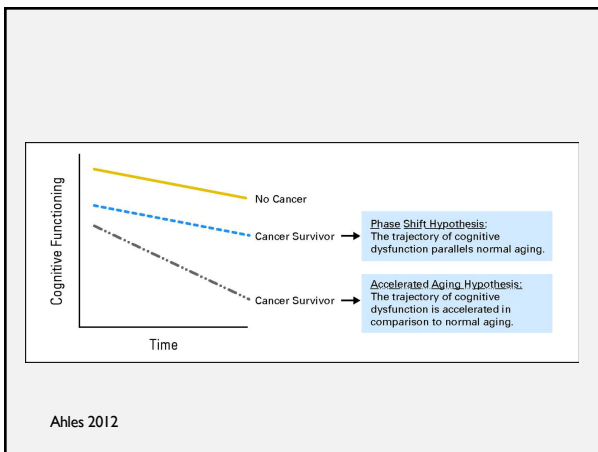
INFLAMMATION

- Associated with ↑ risk for cancer and neurocognitive disorders
- ↑ cytokine levels in CA pts at baseline relative to controls
- ↑ during chemo and ↓ (but stay elevated) with time
- Correlate with self-reported and objective cognitive function
- Correlated with hippocampal volume and metabolism
- Strongest data for TNF α , IL-6, and IL-1 β

Ganz 2013, Janelins 2012, Patel 2015, Wang 2016, Kesler 2013, Lyon 2016



- ### CANCER TREATMENT AND AGING
- Chronic inflammation
 - Increased oxidative stress
 - Accumulation of DNA damage
 - Shortening of telomeres
 - Increased cell senescence
 - Increased expression of p16INK4a and ARF in breast cancer patients (estimated 10 yrs of aging)
 - Increased activation of ERK and AKT signaling pathways in rats
- Sanoff 2014, Salas-Ramirez 2015



CANCER

- Non-CNS Cancers
 - Immune system dysfunction → disrupt brain structure and function
 - Feeling physically ill, fatigued, depressed, etc.
- Primary brain tumors and brain metastases
 - ↑ Intracranial pressure
 - Edema
 - Displacement of brain tissue
 - ↓ blood supply

CHEMOTHERAPY

- Toxic to neural progenitor cells
- Most chemo cannot cross the BBB
 - CA increases BBB permeability
 - Even small amounts can cause significant damage
- Chemo elevates levels of pro-inflammatory cytokines
- Elevated cytokines can lead to damage through oxidative stress and DNA damage
- Once a neuron dies, it is gone forever
- Accelerates brain aging

Wefel 2008, Koppelmans 2012, Deeken 2007, Ahles 2007, Dietrich 2010, Wingmore 2010, Siegers 2009, Siegers 2008, Winocur 2006, Han 2008, Janelins 2012, Puszta 2004, Tsavaris 2002, Collado-Hidalgo 2006, Lynch 2010, Aluise 2011, Joshi 2010, Joshi 2007, Tangpong 2007, Tangpong 2006, Conroy 2013, Sanoff 2014

SURGERY

- In pts w/ brain tumors, can improve or worsen cognitive function
- Mastectomy implicated in cognitive effects
- May be 2/2 increased inflammation and pain
- Impact of anesthesia
 - May be dose-dependent
 - Should last < 6 mo

Schilder 2010, Deboss 2009, Newman 2007, Caza 2008, Vacas 2013, Wang 2007

RADIATION

- Cranial, Head & Neck
 - Radiation necrosis
 - Disrupts creation of new neurons in the hippocampus
 - Accelerate brain aging, increase risk of dementia
- Local
 - Some evidence for adverse cognitive effects
 - May act through DNA damage, inflammation

Phillips 2012, Monje 2003, Monje 2002, Daams 2012, Donovan 2005, Jim 2009

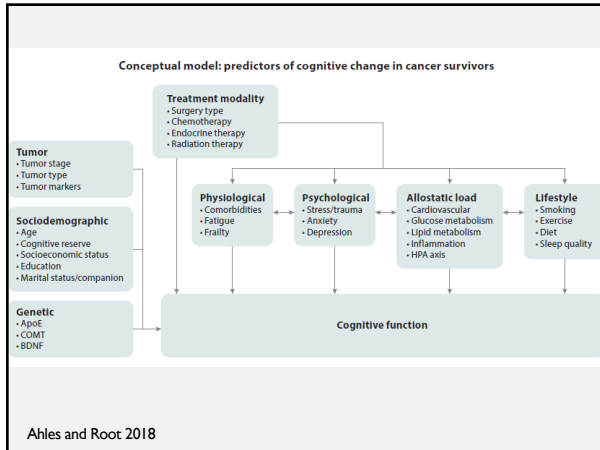
HORMONAL THERAPY

- Estrogen and testosterone support brain function
- Tamoxifen
 - Smaller hippocampal size
 - Combination with chemo may lead to greater cognitive difficulties
 - Other studies show no association
- Aromatase inhibitors independently associated with cognitive decline
- ADT

Collins 2009, Castellon 2004, Schilder 2010, Palmer 2008, Schilling 2003, Ahles 2010, Eberling 2004, Cherrier 2009, Cherrier 2010, Castellano 2011, Bender 2007, Bender 2015

COMORBIDITIES AFFECTING COGNITIVE FUNCTION

- Sleep disorders (insomnia, sleep apnea)
- Depression, anxiety, distress
- Pain and pain medications
- Other physical illnesses
- Fatigue



SELF-REPORT VS. OBJECTIVE MEASUREMENT

- Self-reported problems more common
- Self-report limitations
 - Is it really measuring cognitive impairment?
- Objective measurement limitations
 - Is it sensitive enough?
 - Logistically feasible?

MEASUREMENT OF CRCI

- No standard for screening, monitoring
- Self-report measures: **FACT-Cog, PROMIS Cognitive Function, EORTC-QLQ-30, PRO-CTCAE**
- ICCTF recommends
 - **Hopkins Verbal Learning Test**
 - **Trail Making Test**
 - **Controlled Oral Word Association Test**
- Objective screening instruments: **MMSE, MOCA, RBANS**

EVALUATION

- Self-report screeners
- Screening Instruments
 - Psychiatry, Psychology
 - Occupational Therapy
 - Speech Therapy
- Neuropsychological Assessment
 - Neuropsychologists in PM&R, Neurology, Psychiatry

**FUNCTIONAL, PSYCHOSOCIAL,
AND DEMOGRAPHIC
VARIABLES ASSOCIATED WITH
COGNITIVE SCREENING IN
CHEMOTHERAPY NAÏVE
BREAST CANCER PATIENTS**

Nakamura, Z.M., Deal, A.M., Nyrop, K.A., Choi, S-K., Wood, W.A., Muss, H.B.
Psychooncology 2019 Jan;28(1):167-173.

STUDY DESIGN

- 331 stage I-III breast cancer
- University of North Carolina Hospitals
- 2009-2018
- Completed the Cancer-Specific Geriatric Assessment prior to chemotherapy

MEASURES

- Cognition (BOMC)
- Functional status
 - Patient-reported Karnofsky
 - MOS Physical Function
 - OARS IADL
 - Falls
 - Time Up and Go
- Depression & Anxiety (Mental Health Inventory)
- Social Function & Support (MOS)
- Nutrition (BMI, % weight loss in last 6 mo)

OBJECTIVES

1. Evaluate the use of the BOMC to establish baseline of cognitive function in breast CA pts prior to chemotherapy
2. Describe association between baseline BOMC with wide array of functional, psychosocial, medical, and socio-demographic variables

BLESSED ORIENTATION MEMORY CONCENTRATION TEST (BOMC)

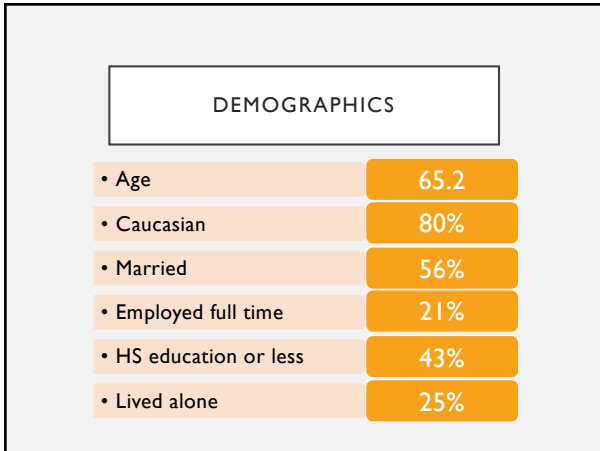
- 6-items
- < 5 min
- Range 0-28; higher is worse cognition
- Developed for dementia (cut point ≥ 11)
- Unclear if sufficiently sensitive to be used to screen for or to monitor CRCI
- Potentially compatible with a busy oncology practice

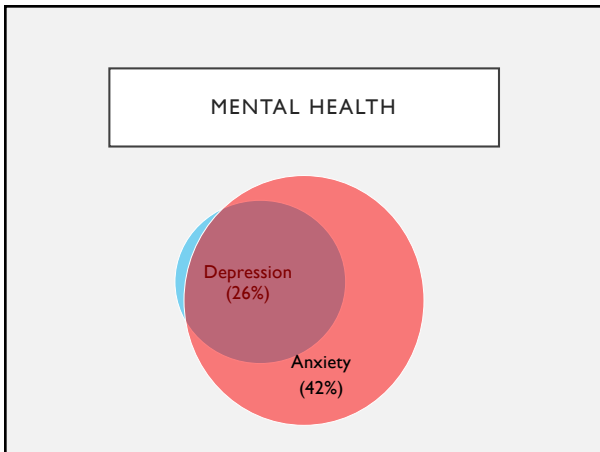
Katzman et al. 1983

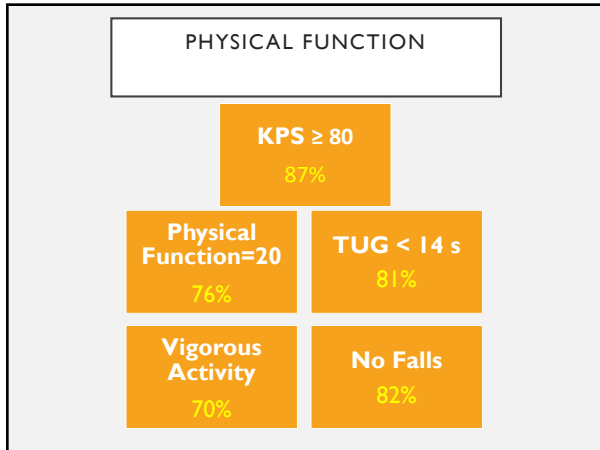
IV) Cognition: Orientation-Memory-Concentration Test

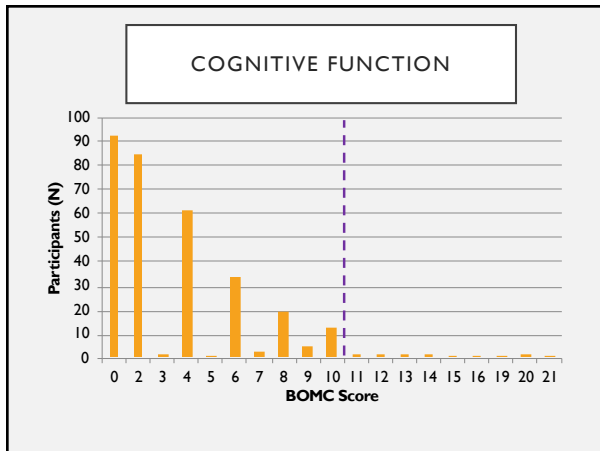
	Patient's response	Maximum errors	Score	Weight	Final Score
1. What year is it now? [without looking at a calendar]	<input type="text"/>	1	<input type="checkbox"/>	x 4 =	<input type="text"/>
2. What month is it now? [without looking at a calendar]	<input type="text"/>	1	<input type="checkbox"/>	x 3 =	<input type="text"/>
Memory phrase Repeat this phrase after me: "John Brown, 42 Market Street, Chicago."					
3. About what time is it? ² [within 1 hour - without looking at your watch]	<input type="text"/> : <input type="text"/>	1	<input type="checkbox"/>	x 3 =	<input type="text"/>
4. Count backwards from 20 to 1.		2	<input type="checkbox"/>	x 2 =	<input type="text"/>
5. Say the months in reverse order.		2	<input type="checkbox"/>	x 2 =	<input type="text"/>
6. Repeat the memory phrase.		5	<input type="checkbox"/>	x 2 =	<input type="text"/>
Total Score =					<input type="text"/>
Incomplete					<input type="checkbox"/>

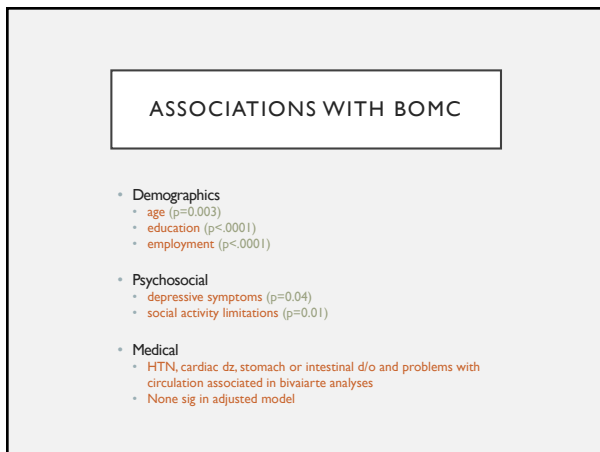
Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, subtract one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Total score of 11 or greater indicates cognitive impairment; please notify MD and assist patient in completing questionnaires. Maximum score = 28











BOMC AND PHYSICAL FUNCTION

- KPS < 80 (p=0.01)
- Physical function score < 20 (p=0.0006)
- IADL < 14 (p=0.02)
- TUG > 14 s (p=0.001)
- Unable to engage in vigorous activity (p=0.009)

IMPLICATIONS

- Concern for cognitive impairment should raise concern for deficits in physical function and vice versa
- Explore interventions that simultaneously target both cognitive and physical function

INTERVENTIONS FOR CRCI

- Behavioral: Cognitive rehabilitation, Cognitive Training, Cognitive Behavioral Therapy
- Physical activity: Yoga, Exercise programs
- Mind-Body: Meditation, Mindfulness, Acupuncture
- Pharmacotherapies: Donepezil, Memantine, Modafinil, Methylphenidate, Ep-stimulating agents, Vitamin E, Ginkgo biloba

INTERVENTIONS FOR CRCI

- Mostly limited to breast CA
- Generally years after completion cancer treatment
- Small sample sizes
- Prevention trials are rare
- Challenges with access, cost, patient participation

COGNITIVE TRAINING

- Repetitive, increasing challenging tasks (often via computer) to improve, maintain, or restore cognitive function
- Has been tested in 5 studies
 - Primarily in early stage breast CA survivors
 - Completed adjuvant therapy and were reporting cognitive concerns
- Start out with 4-5, 30-60 min sessions per week for at least 6 weeks

Damholdt 2016, Bray 2016, Kesler 2013, Meneses 2018, Von Ah 2012

COGNITIVE REHABILITATION

- ↑ self-awareness to support problem-solving and compensatory strategies
- Mostly used in TBI and stroke populations
- Research
 - Individual and group delivery (in person or online)
 - 4-7 sessions
 - Improved cognitive symptoms but not neuropsychological performance
- Usually weekly therapy for 30-60 min with neuropsychologist, occupational therapist, speech/language pathologist
- Not widely available or covered by health insurance
- CPT codes: 97532, 97535, 97537

Cherrier 2014, Ercoli 2015, Green 2018, King 2015, Mihuta 2018, Schuurs, 2012, Becker 2017, Ferguson 2007, Ferguson 2016, Park 2017

PHYSICAL ACTIVITY

- ↑ new neurons in the hippocampus, BDNF levels, reduces inflammation
- ↓ risk of Alzheimer's and slows age-related cognitive decline
- Moderate intensity exercise (60% max HR - walking, yoga, dancing, stair climber, weight lifting) at least 150 min/week or vigorous exercise (70% max HR - jogging, running, boxing) at least 120 min/week
- Local Resources
 - Get REAL & HEEL - Individualized exercise combined with psychosocial therapy (e.g. pain and stress management, relaxation techniques, mindfulness training, etc.), 3x/week x 16 wk, Free
 - LIVESTRONG at the YMCA - 12-week program, 10 ppl/class, Raleigh, Durham, Sanford, Chapel Hill
 - Live Fit Cancer Exercise Program
 - Yoga - Wholistic Health Studio, F,\$50 for 12 classes, CCSP Yoga (MW \$5/class), Breast Cancer Survivor Yoga Series at Carolina Yoga Company

Zimmer 2016, Myers 2018, Curlik 2013, Kramer 2006, Speisman 2013, Pietrelli 2012

MIND-BODY

- Bring an awareness of individual potential for healing or restoration
- Guided imagery, meditation, mindfulness-based stress reduction, neuro/biofeedback, and acupuncture
- Mindfulness
 - UCLA MAPS classes - 6-wk online courses - www.marco.ucla.edu
 - Apps: The Mindfulness App (I&J), Sitting Still, Headspace, Insight Timer, Mindfulness Bell
 - Local courses through UNC-Chapel Hill Program on Integrative Medicine and Duke Integrative Medicine
- Acupuncture
 - UNC Family Medicine Acupuncture Clinic
 - NC Society of Acupuncture and Asian Medicine (www.ncsaam.org/Find-a-Local-Acupuncturist)

Freeman 2014, Milbury 2013, Hoffman 2012, Johns 2016, Alvarez 2013, Johnston 2011, Cimprich 1993, Cimprich and Ronis 2003

PHARMACOTHERAPIES

- Stimulants (methylphenidate and modafinil)
- Alzheimer's drugs (donepezil and memantine)
- SSRIs (sertraline and paroxetine)
- Ginkgo biloba
- Vitamin E
- Erythropoietin-Stimulating agents*
- Weigh risk/benefit

Gehring 2012, Meyers 1998, Kohli 2009, Shaw 2006, Correa 2015, Rapp 2015, Lawrence 2016, Brown 2013, Chan 2004, Actia 2012, Li 2014, Lunderoff 2009, Chang 2004, Massa 2005

FOR ALL PATIENTS

- Active journaling
 - Describe an experience, why it was important, what it meant for you, what you learned from it
 - Goal to increase "idea-density"
- External aids
 - Day planner
 - Alerts/reminders on smart phone or tablet
 - Sticky notes, whiteboards
- Routine
- Workplace accommodations
 - Examples and procedural information available at www.eeoc.gov/policy/docs/accommodation.html



IMPROVING
COGNITIVE FUNCTION
AFTER CANCER
Shelli Kesler, PhD

UNC COMPREHENSIVE CANCER
SUPPORT PROGRAM (CCSP)



<https://unclineberger.org/ccsp/>
