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Late andLong term side effects of chemotherapy

Richard van der Jagt

Non-Hodgkin Lymphoma (C82-C85): 2010-2011

One-, Five- and Ten-Year Net Survival (%), Adults Aged 15-99, England & Wales

		1-Year Survival (%)	5-Year Survival (%)	10-Year Survival (%)
Men	Net Survival	79.7	68.2	62.4
	95% LCL	79.7	68.1	62.2
	95% UCL	79.7	68.3	62.6
Women	Net Survival	79.4	69.5	64.1
	95% LCL	79.4	69.4	63.8
	95% UCL	79.5	69.6	64.3
Adults	Net Survival	79.6	68.8	63.2
	95% LCL	79.6	68.7	63.0
	95% UCL	79.6	68.8	63.4

Five- and Ten-year survival has been predicted for patients diagnosed in 2010-2011 (using an excess hazard statistical model)
95% LCL and 95% UCL are the 95% lower and upper confidence limits

Please include the citation provided in our Frequently Asked Questions when reproducing this chart:
http://info.cancerresearchuk.org/cancerstats/faqs/#How
Prepared by Cancer Research UK
Original data sources:
Survival estimates were provided on request by the Cancer Research UK Cancer Survival Group at the London School of Hygiene and Tropical Medicine. http://www.lshtm.ac.uk/eph/ncde/cancersurvival/

CANCER RESEARCH UK

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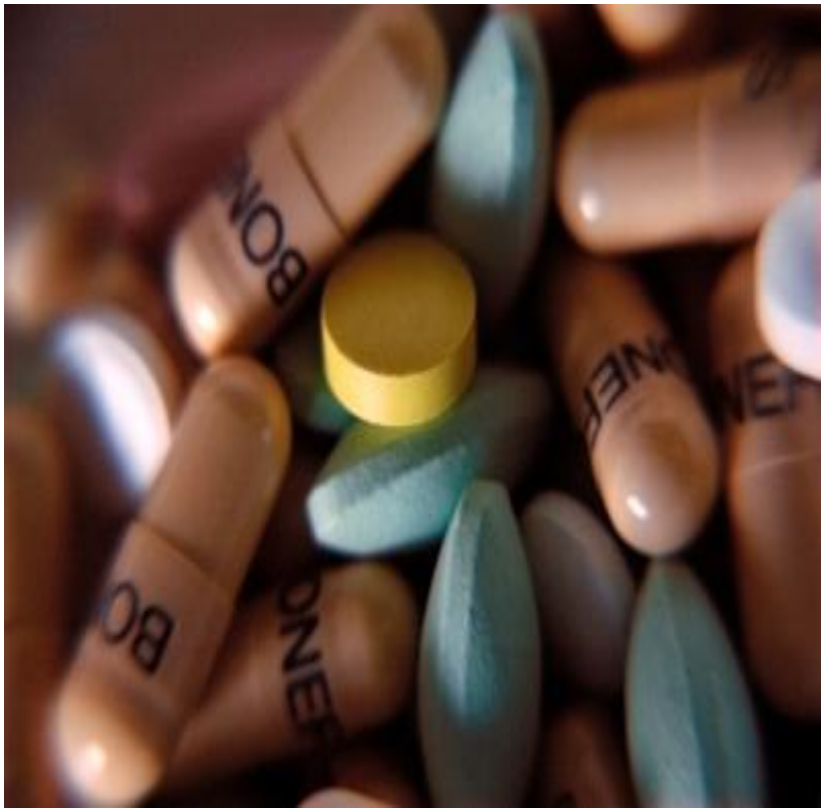
Chemo Fog: Let's Clear the Air

Barbara Collins, Cheryl Harris, Richard van der Jagt

Introduction

- Growing number of cancer survivors due, in part, to increased use of chemotherapy as adjuvant therapy, more aggressive dosing schedules
- Survival comes at a cost--increasing recognition of long-term side-effects of cancer treatments
- *Chemo fog/chemobrain* may be among these adverse effects



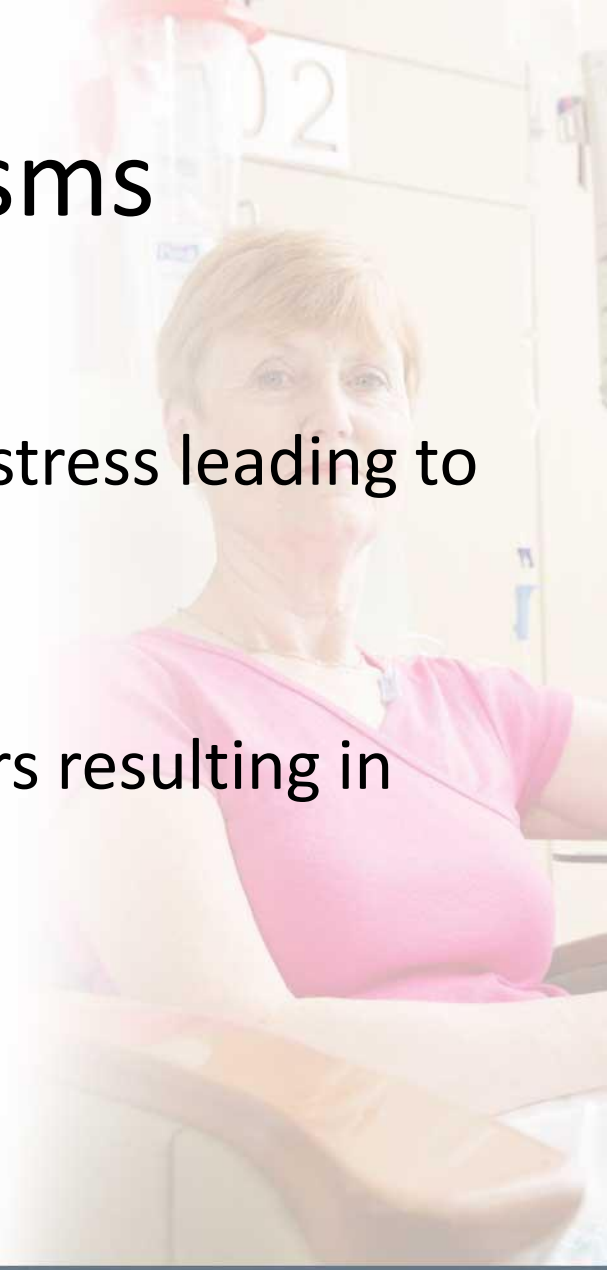
What is "Chemo Fog"?

- Mild cognitive impairment that typically arises during systemic adjuvant chemotherapy for non-CNS cancers
- Increase in the frequency of "everyday slips and lapses"
- Multi-factorial→ CRCI
- Subtle but significant implications for IADLS & QOL, capacity/informed consent, disability, drug development

Superman in his later years

Possible Mechanisms

- Direct neurotoxicity
- Cytokine dysregulation → Oxidative stress leading to DNA damage in neuronal cells
- Microvascular injury
- Interference with nerve growth factors resulting in suppression of neurogenesis
- Neurochemical alterations



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NP Studies

Cross-Sectional Studies

- ~ 80% find CT-treated patients perform more poorly than controls
- Seen as long as 20 years post treatment

Issues

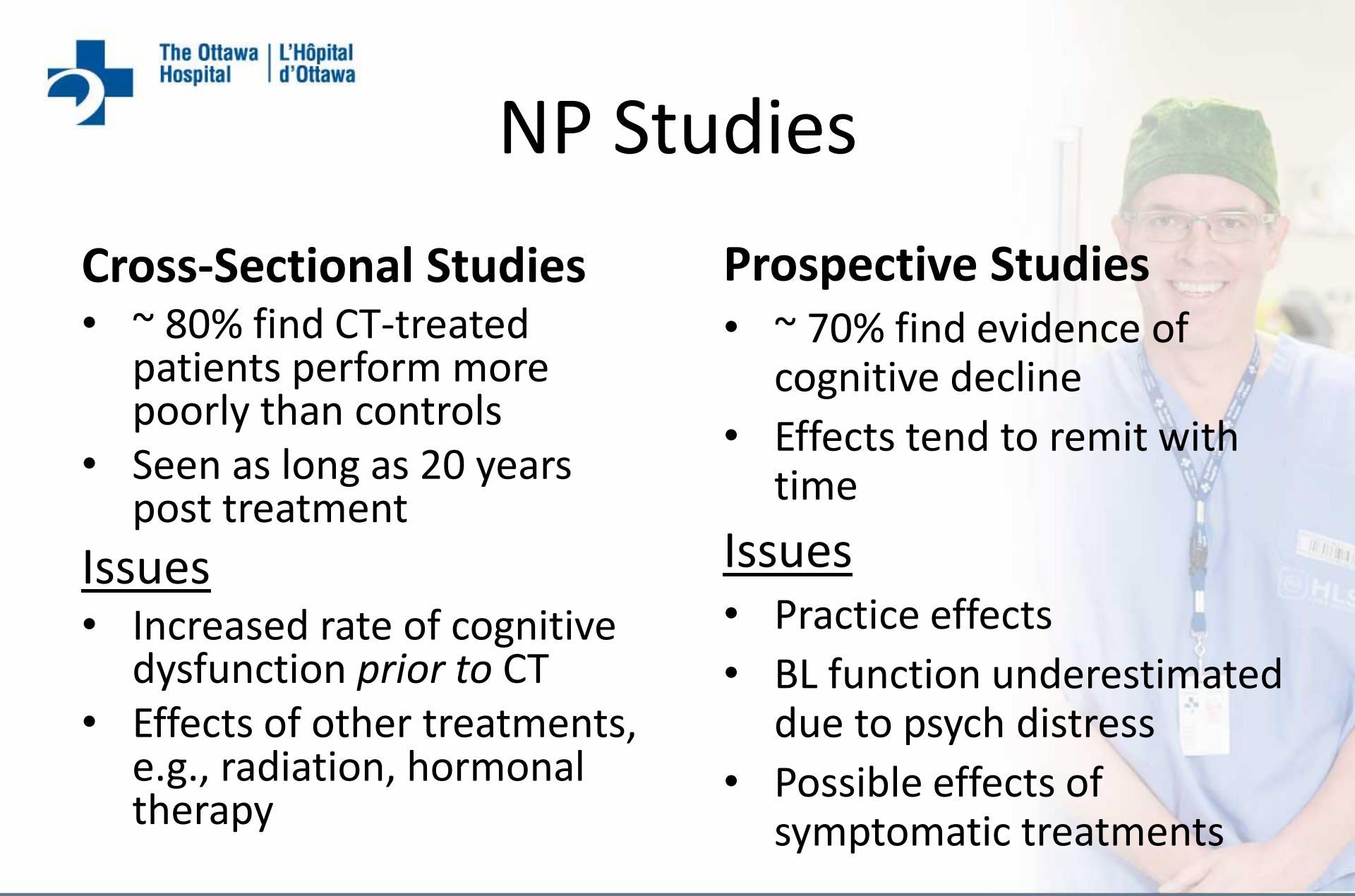
- Increased rate of cognitive dysfunction *prior to* CT
- Effects of other treatments, e.g., radiation, hormonal therapy

Prospective Studies

- ~ 70% find evidence of cognitive decline
- Effects tend to remit with time

Issues

- Practice effects
- BL function underestimated due to psych distress
- Possible effects of symptomatic treatments



Initial Prospective Longitudinal Study of NP function in BC patients

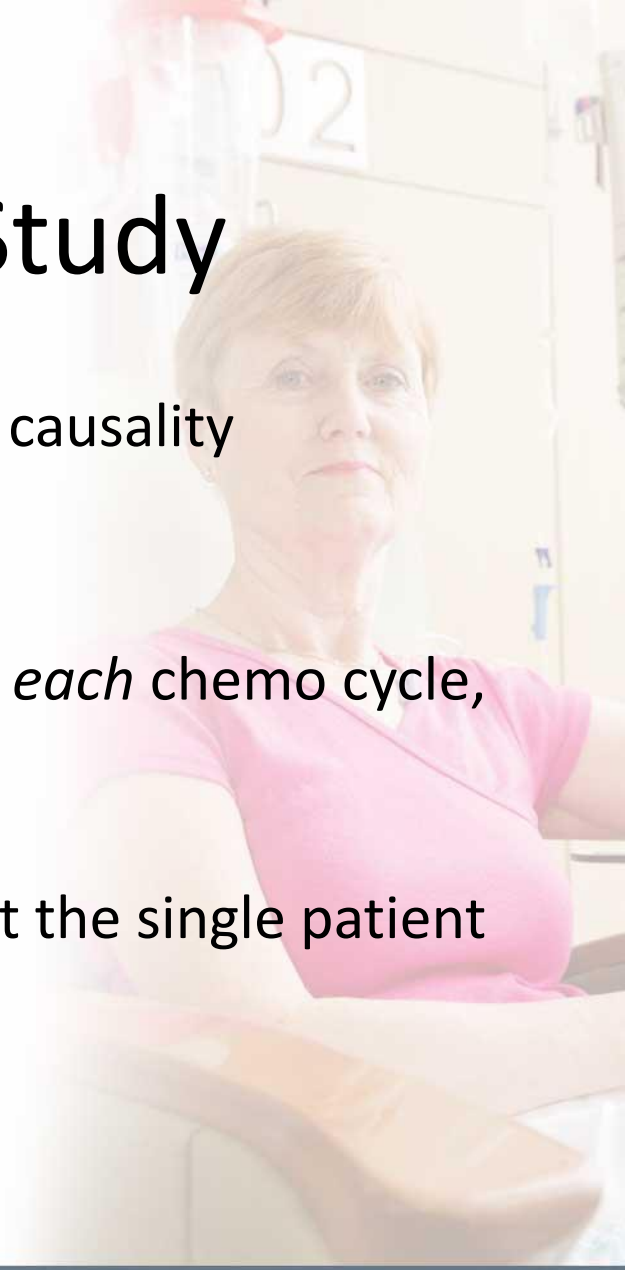
- BC patients receiving chemo or hormonal therapy assessed pre-tx, immediately post-tx, and 1 year post tx
- 30% of chemo patients showed "reliable cognitive decline" from pre- to post-tx (3X as many as hormonal group)
- Subtle
- *Working memory* particularly affected
- Remitted over time
- Still confounded because treatment is inextricably linked to disease and host characteristics

"Dose-Response" Study

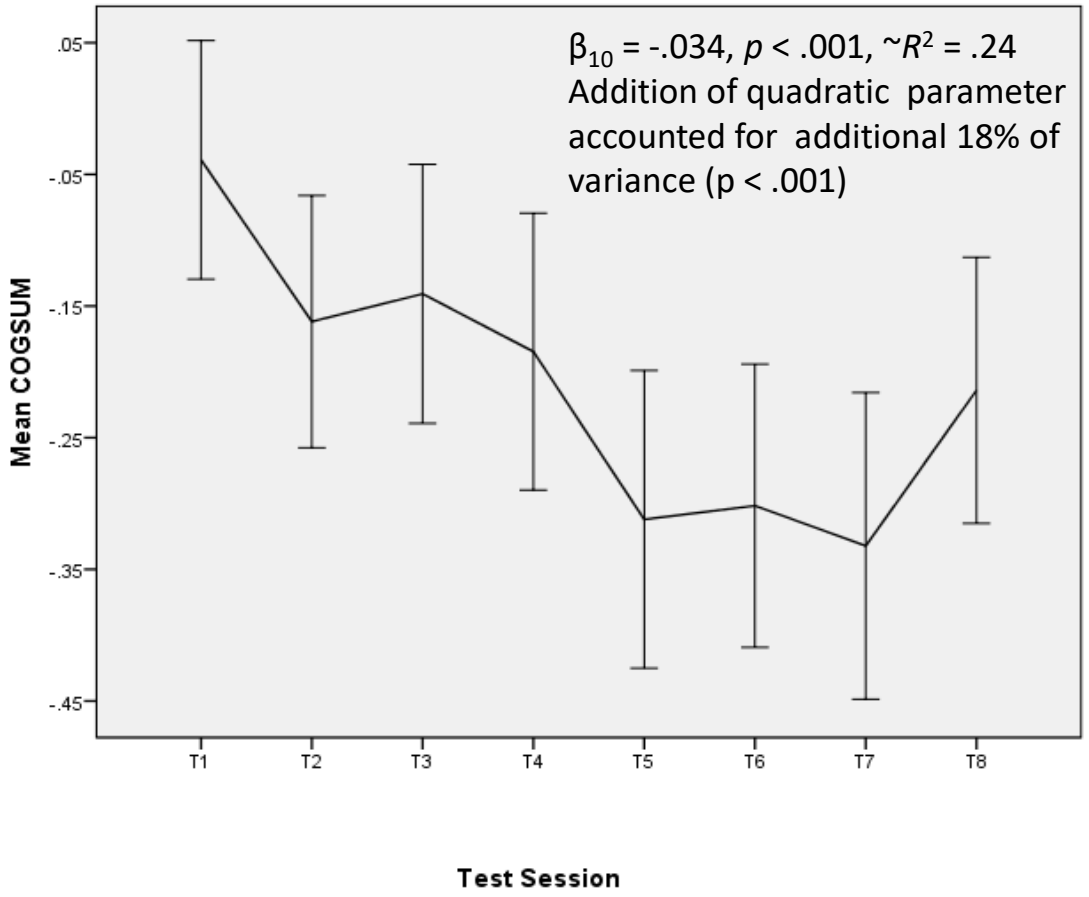
Aim: Dose-response approach to establishing causality

Method:

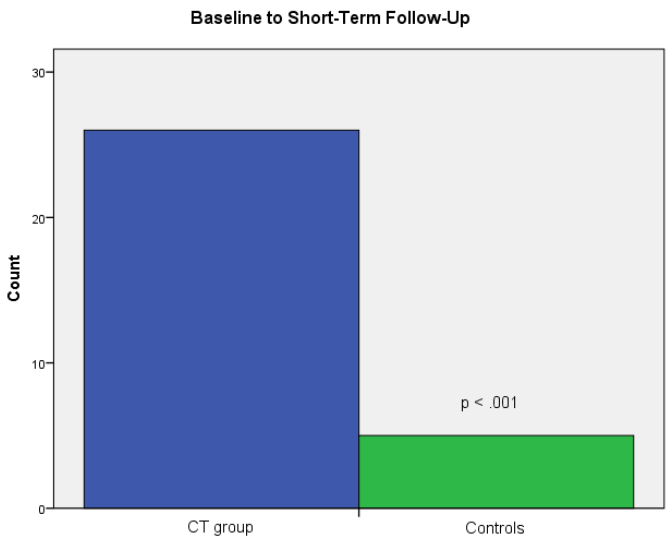
- Cognitive testing done before Tx, following *each* chemo cycle, and 1 year post Tx
- MLM to assess change at the group level
- individualized approach to assess change at the single patient level

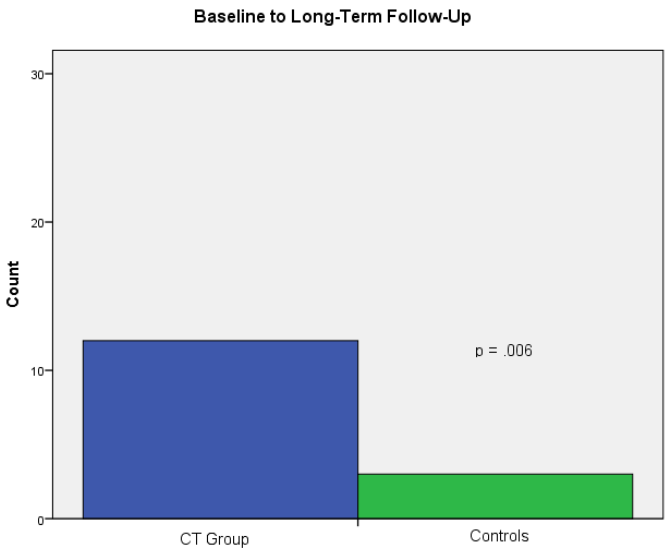


Change in COGSUM (overall summary of test scores) over testing sessions in BC patients based on battery of neuropsychological tests

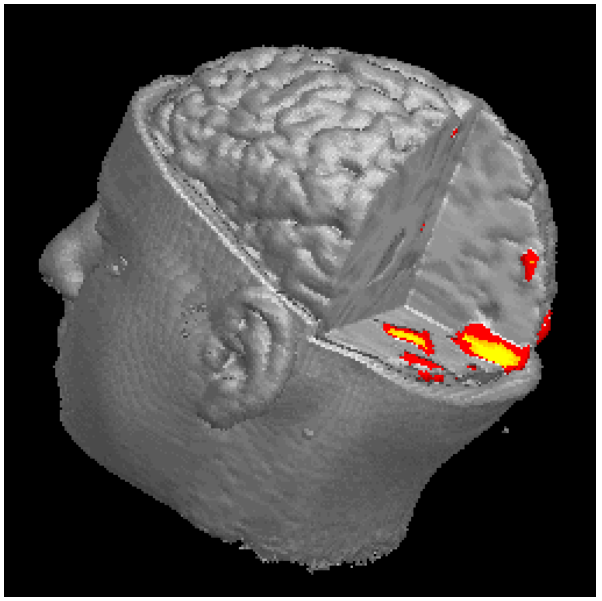


Frequency of Decline in CT and Control Groups





MRI



Pretreatment

- Differences in white matter volumes in frontal, parietal and limbic regions
- Differences in neural activity for all 4 tasks, particularly in the prefrontal cortex

Immediate post-treatment

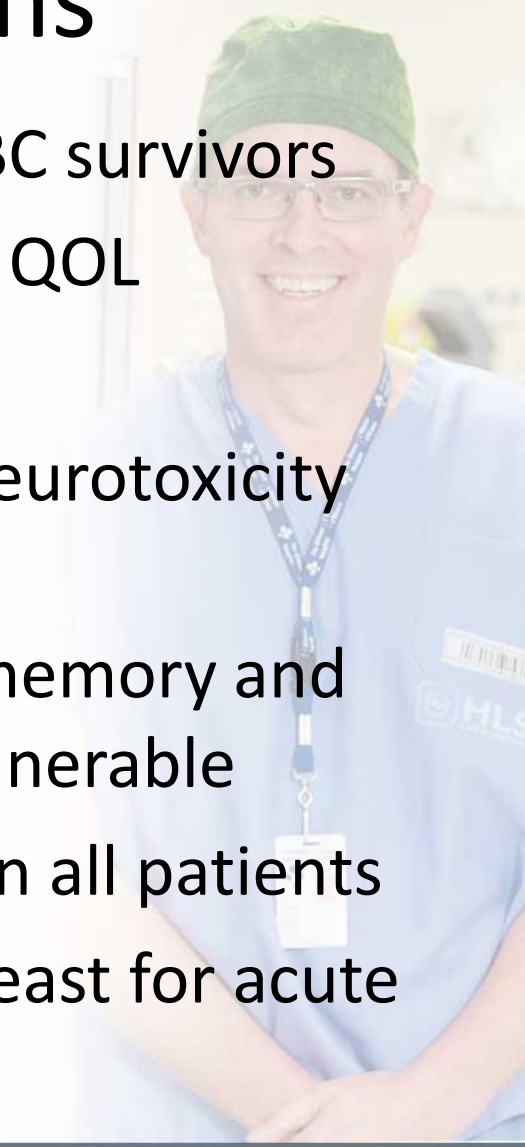
- Reduced white matter volume in region of L caudate
- Reduction in FA in BC patients in: L frontal white matter; L anterior body of corpus callosum; Broca's area; R medial thalamus; R brachium pontis; cerebellar white matter

One-year follow-up

- Persistent reductions in FA, but less prominent and accounted

General Conclusions

- Cognitive changes are common among BC survivors
- Subtle but can affect complex IADLs and QOL
- Multi-factorial → *Cancer Fog*
- Accruing evidence that chemotherapy neurotoxicity one contributing factor
- Different abilities affected but working memory and processing speed may be particularly vulnerable
- Remit with time, but not completely or in all patients
- Amount of CT exposure a risk factor, at least for acute effects



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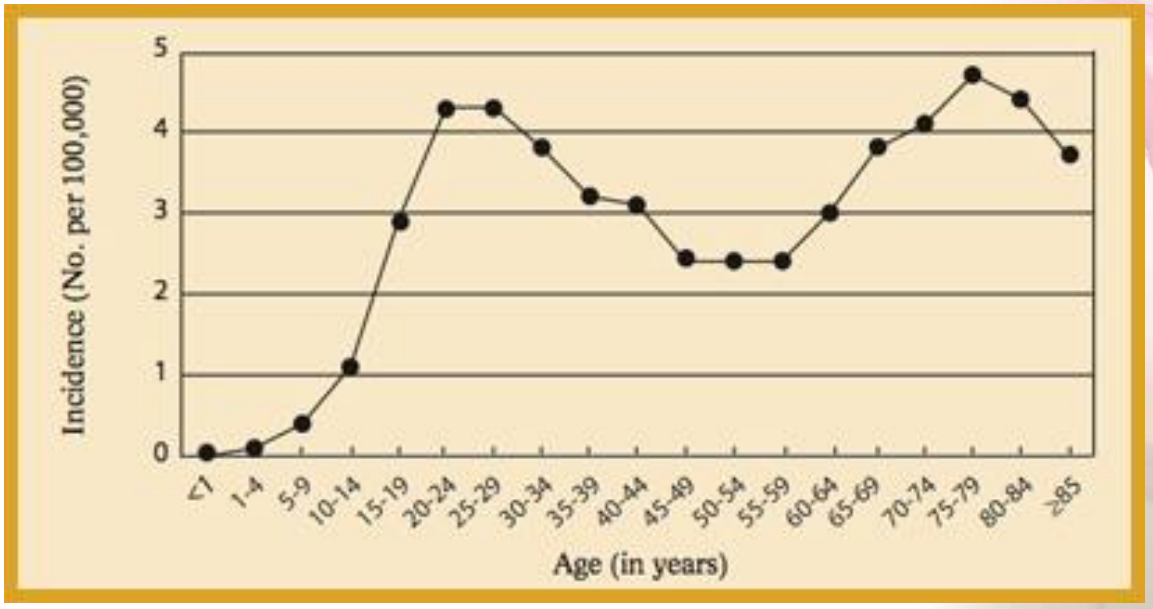
Cognitive Disturbance in Lymphoma Survivors: Correlations with Chemotherapy Exposure, Fatigue, and Psychological Distress

Rationale

- ICCTF emphasizes need to extend CRCI research to other cancer populations
- In 2010, about 628,000 people living with lymphoma or are in remission
- Peak age of onset in young adults and older individuals (CCS, 2009)



Other Psychosocial Factors and CRCI: Fatigue

- Prevalence estimates of fatigue from 70% to 100% across all cancer populations
- For many patients, most distressing side-effect of cancer, causing most disruption of normal functioning
- Documented in disease-free survivors up to 10 years post-treatment
- Multifactorial etiology—interplay of physical, mental, emotional, environmental, physiological and pathological factors
- Fatigue associated with CRCI in some studies but cannot fully account for objective cognitive disturbances

Other Psychosocial Factors and CRCI

- Depression and anxiety also posited as factors in CRCI
- Studies in BC patients generally find that they are strongly associated with subjective cognitive measures but weakly, if at all, correlated, with objective cognitive performance
- Subjective and objective measures of cognitive function themselves poorly correlated
- Pain and insomnia also common among cancer survivors and can result in cognitive disturbances

CRCI in Lymphoma

Primary CNS lymphoma

Doolittle et al., 2013 *(Neurology 81:84-92)*

- 12% of survivors in complete remission without WBRT (just HD CT) had cognitive impairment in multiple domains
- In whole sample, global QOL score associated with global NP score

CRCI in Lymphoma

HSCT

- Several studies report increased frequency of subtle cognitive dysfunction in hematological ca pts post-HSCT

Correa et al., 2013 *(Brain Imaging Beh 7:478-490)*

- 21% of patients met criteria for cognitive impairment at baseline – consistent with literature reporting dysfunction in 20-40% prior to transplant—chemotherapy-related?

CRCI in Lymphoma

Devlen et al., *1987* *(Br Med J 295:953-957)*

- Surveyed patients with Hodgkin's or non-Hodgkin's lymphoma treated with radiotherapy and/or chemotherapy 2.7 years post-dx; mostly disease free and off treatment
- ~1/3 of sample (30/90) complained of impairment in thinking or short-term memory
- Second in frequency only to lack of energy

CRCI in Lymphoma

Ahles et al. 2002 *(J Clin Oncol 20(2):485-93)*

- Long term survivors of breast cancer or lymphoma treated with chemotherapy vs local therapy only
- Chemotherapy group performed more poorly on battery of neuropsychological tests and self-report of working memory – same effect in both breast and lymphoma

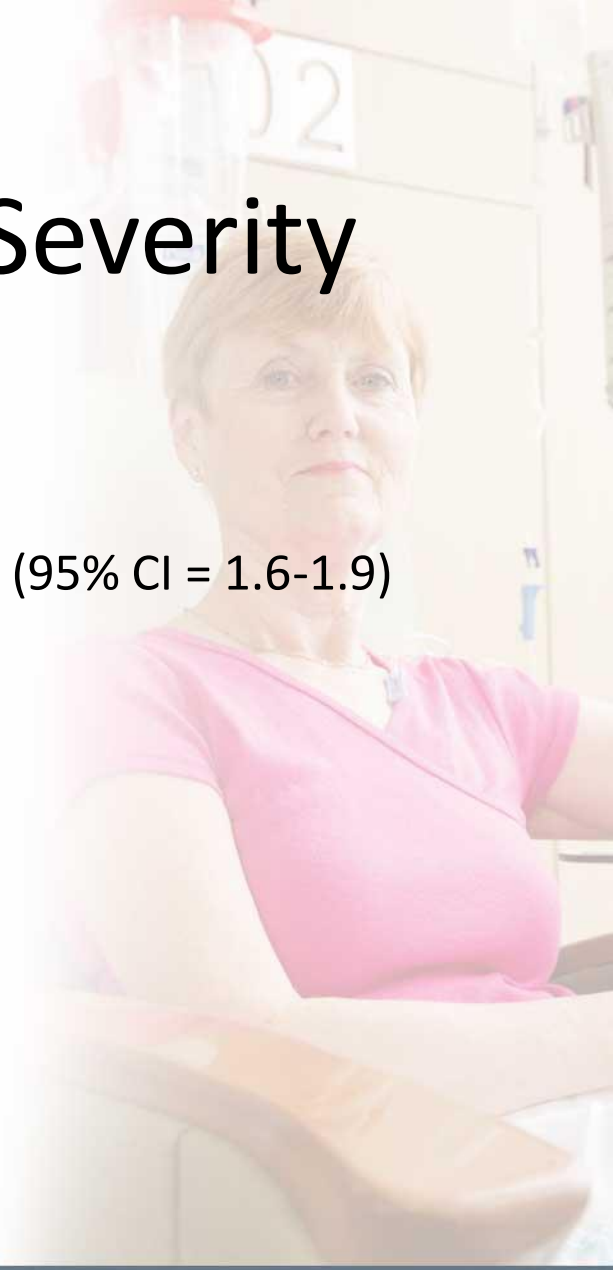
Methods

- Questionnaire package mailed to 622 patients treated for lymphoma at TOH in past 5 years (Medical-demographic questionnaire, FACT-Cog, PHQ-9, GAD-7, FACT-F, ISI, BPS, QOL Rating)
- Questionnaires returned = 330
- Questionnaires analyzed =248
- Computerized cognitive testing = 99

Participants

- 53% male
- 87% Caucasian
- 70% had some college or university
- 50% employed
- Mean age = 54.7 (SD 13.8, rg 21-76)
- Time since last tx 2.6 years
- 87% received CT

Results: Frequency & Severity



PHQ-9

- 22% ≥ 8 → 5.5% MDD
- Estimated Prevalence in general population = 1.8% (95% CI = 1.6-1.9)

GAD-7

- 10% ≥ 10 → 3.0% GAD
- Est Prevalence in general population = 1.5-3%

ISI

- 47% ≥ 8 → 37% clinical insomnia
- Est Prevalence in general population = 13.4%

Avg of 4 NRS on the BPI

- 10% reported moderate or severe pain

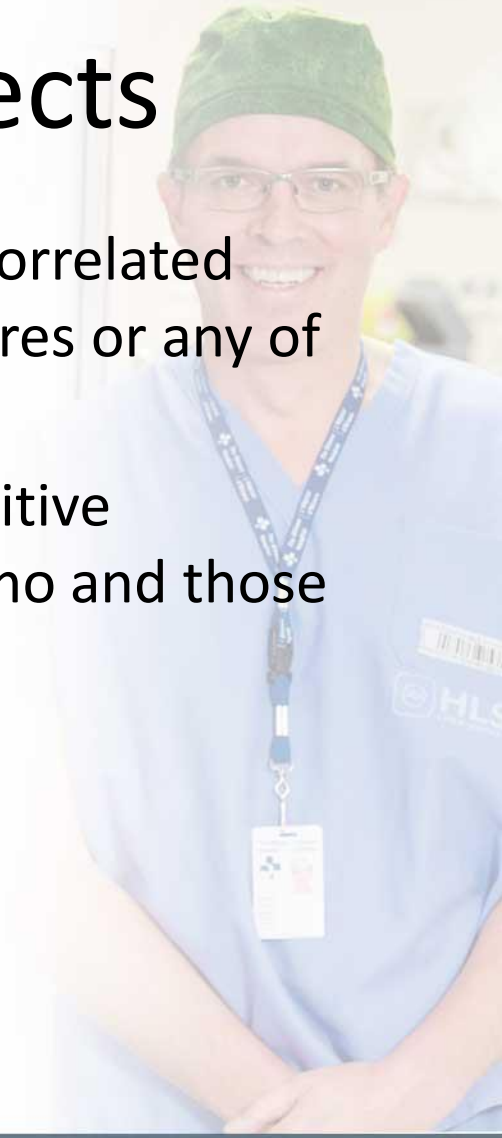
Results: Frequency & Severity

Table 1. Percentage of lymphoma patient sample reporting clinically significant fatigue, cognitive symptoms, and impact of cognitive symptoms on quality of life and showing objective cognitive dysfunction compared to healthy samples

	Number (Percentage)	χ^2	**Significance**
Fatigue (Total Score on FACIT-F) (n = 262)	80 (31)	37.9	P < .001
Cognitive Sx (PCI Score on FACT-Cog) (n = 261)	68 (26)	8.2	P = .004
Impact of Cognitive Sx on QOL (QOL score on FACT-Cog) (n = 258)	107 (41)	21.0	P < .001
Objecitve Cognitive Dysfunction (CNS-VS) (n = 99)	7 (7)		ns

Results: Treatment Effects

- Time since last tx, number of chemo tx not correlated with subjective or objective cognitive measures or any of PS variables
- No difference in subjective or objective cognitive measures between those who received chemo and those who did not (but n only 22)



Results: Relationships between Psychologic Factors and Cognitive Function

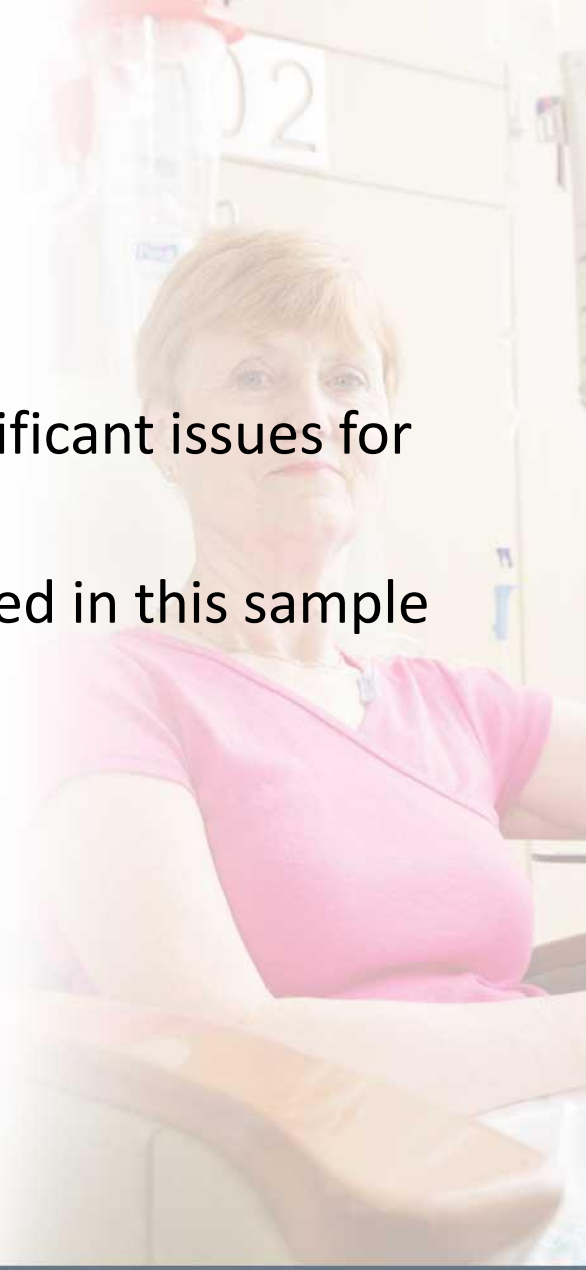
- SW linear regression with subjective cognitive function (PCI) as DV
  - Together fatigue (β = .493) and anxiety (β = -.323) accounted for 55% of the variance
  - Depression, insomnia, and pain were excluded from the model
- SW linear regression with objective cognitive function (CNS-VS total score) as DV
  - Pain (β = -.317) accounted for 9.2% of the variance
  - Anxiety excluded

Results

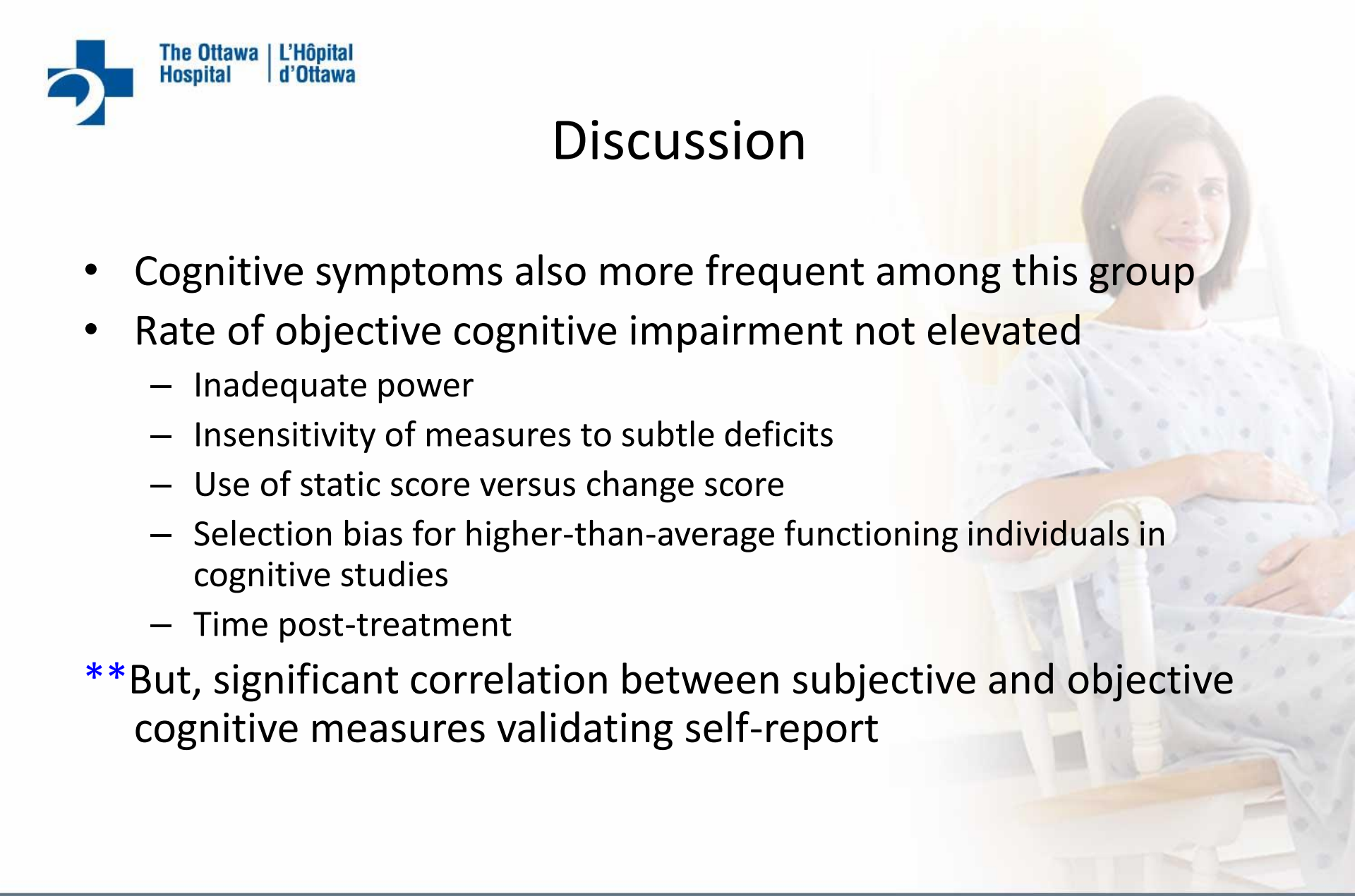
- Significant correlation between Perceived Cognitive Impairment and CNS-Vital Signs total score ($r = 0.29$, $p = .005$) (CNS vital signs score is based on a computerized score of cognitive function)
- Remains significant even after controlling for age and education

Discussion

- Depression, insomnia, fatigue, and pain significant issues for lymphoma survivors
- Frequency of anxiety not significantly elevated in this sample



Discussion



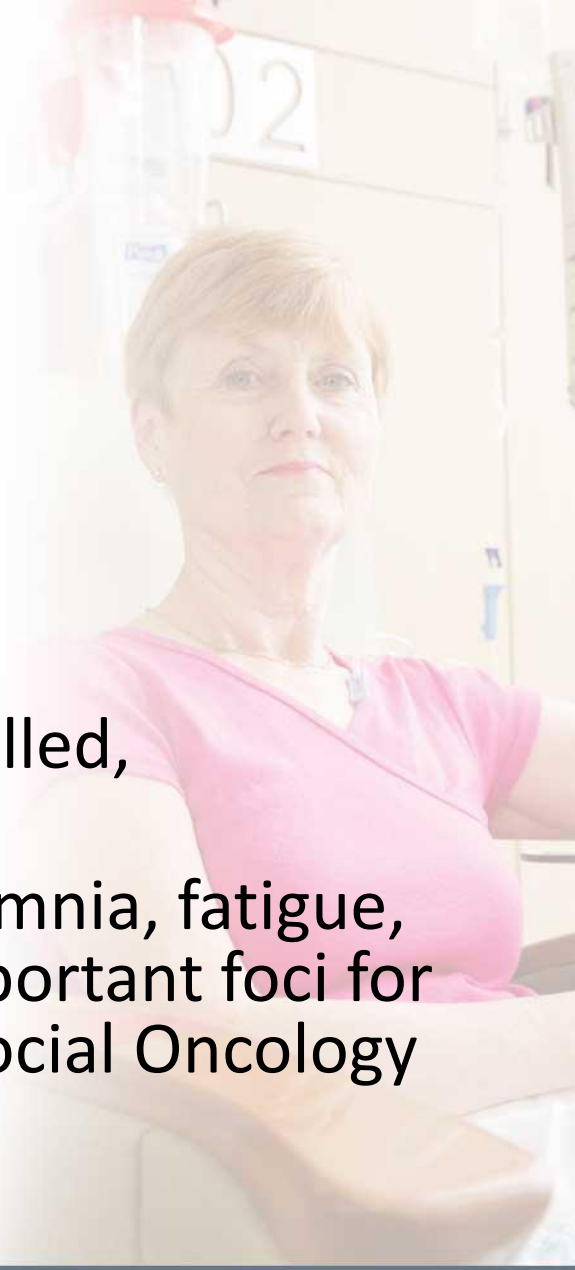
- Cognitive symptoms also more frequent among this group
- Rate of objective cognitive impairment not elevated
  - Inadequate power
  - Insensitivity of measures to subtle deficits
  - Use of static score versus change score
  - Selection bias for higher-than-average functioning individuals in cognitive studies
  - Time post-treatment

**But, significant correlation between subjective and objective cognitive measures validating self-report

Discussion

- Fatigue and cognitive symptoms strongly related
- But, direction of relationship unclear
  - Cognitive sx due to systemic fatigue
  - Fatigue due to neural dysfunction
  - Both cognitive dysfunction and fatigue secondary to other, common mechanism (e.g., decreased hemoglobin, increased cytokines)
- Pain the only psychologic factor significantly related to objective cognitive function
  - Distraction
  - Mobility restrictions?

Conclusions



- Limitations of study
  - Retrospective
  - Uncontrolled
  - Objective cognitive testing limited
- But findings do warrant further controlled, prospective study
- Findings suggest that depression, insomnia, fatigue, pain and cognitive dysfunction are important foci for assessment and treatment in Psychosocial Oncology programs

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Thank You!

- ***Our participants!***
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- ***The team (Breast)***
  Joyce MacKenzie, M Ps
  Andra Smith, Ph D
  Cate Bielajew, Ph D
  Angela Stewart, Ph D
  Carole Scherling, Ph D
  Eva Tomiak, MD
  Shailendra Verma, MD
  Nesrine Awad, Ph D
  Rocio Lopez, BA
  Nancy Wallis, BA
  Lorelle Weiss, M Sc
  Chris Lepage, BA

(Lymphoma) Dr R van der Jagt
Dorothy Krolak
Lorelle Weiss

Second malignancy

1. **Long term survivors are at increased risk for: myelodysplasia, AML**
2. **Several solid tumors including: several solid tumors, including cancers of the bladder, lungs, and GI tract, and neck, thyroid, and CNS; and sarcoma, melanoma, nonmelanomous**
3. **skin cancers, and mesothelioma**
4. **In a British study of 2,456 patients with NHL,60 the RR and AER of all malignancies (excluding nonmelanomatous skin cancers and NHL) were 1.3 (95% CI, 1.1 to 1.6) and 15.4 per 10,000 person-years, respectively.**
5. **In a report that included almost 74,000 patients with NHL in the Surveillance, Epidemiology, and End Results (SEER) program, found that the RR and AER of all subsequent cancers (excluding NHL) were 1.14 (P .01) and 19 per 10,000 person-years, respectively.66**

Risk of Second Malignancy cont'd

1. So far very little increased risk after BR
2. Bladder cancer after NHL has been linked to treatment with cyclophosphamide in a dose-dependent manner, and also to RT.
3. Risk of lung cancer after chemo is modestly increased (<2-3x general population) (? Contribution of prior smoking)

Other complications

- Doxorubicin, a key component of chemotherapy regimens in the treatment of aggressive NHL, is associated with cardiomyopathy and congestive heart failure
- In a retrospective study conducted by the EORTC of 974 patients with NHL treated with six or more cycles of doxorubicin-based chemotherapy
- The RR of congestive heart failure was significantly higher in younger patients, those with hypertension,

and smokers, whereas the RR of myocardial infarction was significantly higher in patients with hypertension

Cardiovascular cont'd

- male sex (P .01), older age (P .01), higher cumulative dose of doxorubicin or treatment with another anthracycline (P .04), RT (either total-body or mediastinal irradiation; P .04), and being overweight (P .04) were significantly associated with decreased ventricular function
- After adjusting for pre-existing cardiac risk factors and prior heart disease, doxorubicin use was associated with a 29% increased risk of congestive heart failure.

Gonadal Dysfunction

- Depending on chemo, a significant reduction in sperm concentration and motility grade was observed, with 59% and 14% of men becoming azoospermic and oligozoospermic, respectively.
- mean recovery time to the highest post-treatment sperm concentration was 45 months, with a significantly longer recovery period in men with the greatest reduction in sperm concentration immediately after treatment.
- The fertility status of 36 women during therapy, 18 patients(50%) developed amenorrhea, six (17%) had irregular menstrual cycles, and 12 (33%) continued regular cycles (four received contraceptive pills).

Fertility cont’d

- In 63% of the women with amenorrhea, menstrual function recovered within 3 months

Osteroporosis

- Steroids interfere with bone formation and remodeling resulting in increased fracture risk even for patients, increasing risk for vertebral fractures
- Post CHOP vertebral density did not recover to baseline levels after two years. New vertebral fractures occurred in 16/111 patients (14%)
- Role of bone density scanning?

Peripheral Neuropathy (secondary to vincristine as part of CHOP or CVP

- Pain, burning or tingling in fingers, toes, hands and feet
- Loss of sensation to touch
- Difficulty picking things up or buttoning clothes
- Weakness, cramping or pain in hands and/or feet
- Sensitivity to temperature extremes
- Muscle weakness and balance problems
- Constipation
- Decreased reflexes

Peripheral neuropathy cont’d

- higher risk for developing peripheral neuropathy if you have pre-existing conditions such as diabetes, alcoholism, malnutrition, vitamin B deficiencies
- Symptoms may appear the to be the strongest just after chemotherapy treatment, and can last until many months after treatment has been completed. Symptoms may lessen over time, but it's a gradual process that requires several months to resolve.

Neuropathy cont'd comfort measures

- Splinting and protecting affected area
- Massage, physical therapy, and acupuncture
- Relaxation therapy
- Use of vitamins, especially B vitamins (B-1, B-6, and B-12). Ask your MD about dosing. Vitamin E and niacin are also important to nerve health.
- Gentle laxatives for constipation
- Prescribed medication such as steroids, lidocaine patches, capsaicin creams, anti-depressants, anti-seizure medications, and pain medications

Practical tips:If you have symptoms

- Protect your hands and feet where sensation is decreased (wear good footwear and protect from injury).
- Be aware of temperature changes, such as extreme cold or hot (check water temperature of your shower and bath water, use gloves when doing housework).
- Always check for any cuts, abrasions, burns and injury to hands and feet..

If you have neuropathy

- minimize alcohol; this may make symptoms worse over time.
- •Use handrails, canes and other assistive devices if needed for balance