Understanding and treating cancer-related fatigue

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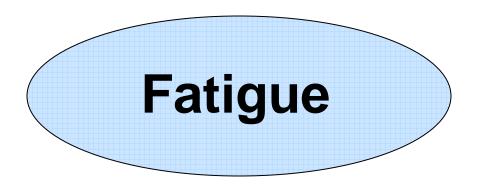


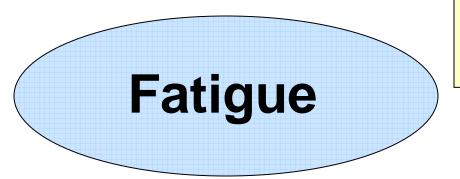
Cancer-related fatigue

- Fatigue is the most common and distressing side effect of cancer and its treatment
- Different than "normal" fatigue due to lack of sleep or overexertion
 - More severe, longer lasting, not relieved by adequate sleep or rest
 - Involves mental, physical, and emotional components

Prevalence of fatigue

- 60 99% of patients report fatigue during cancer treatment
- 25 30% of cancer survivors continue to report fatigue up to 10 years after treatment completion
- Fatigue is associated with significant impairment in quality of life





Demographic factors

- Age
- Income
- Marital status

Fatigue

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- Depression
- Catastrophizing coping style

Fatigue

Health behaviors

Physical activity

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Comorbid symptoms

- Pain
- Menopausal sx
- Sleep disturbance

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Comorbid medical conditions

- •Cardiovascular disease
- •BMI

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Biological factors

- Anemia
- Inflammation

Fatigue

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- Age
- •Income
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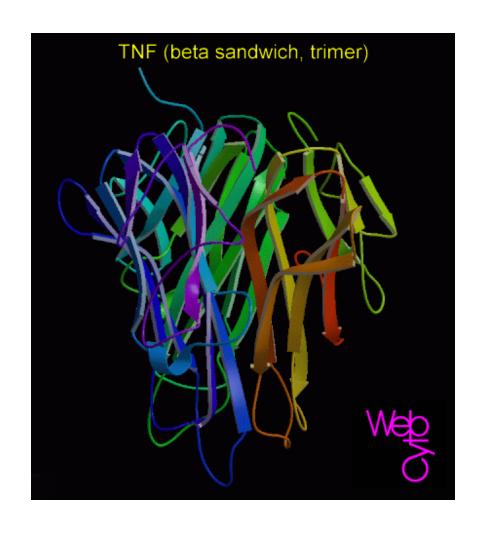
Health behaviors

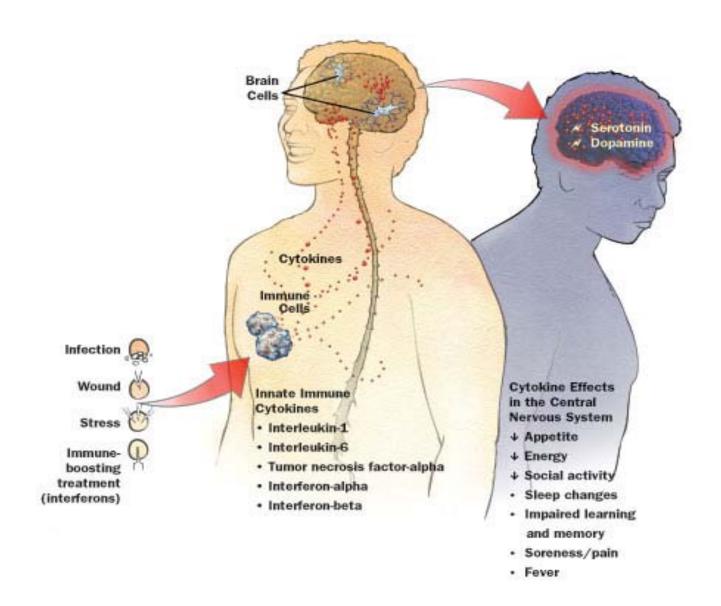
Physical activity

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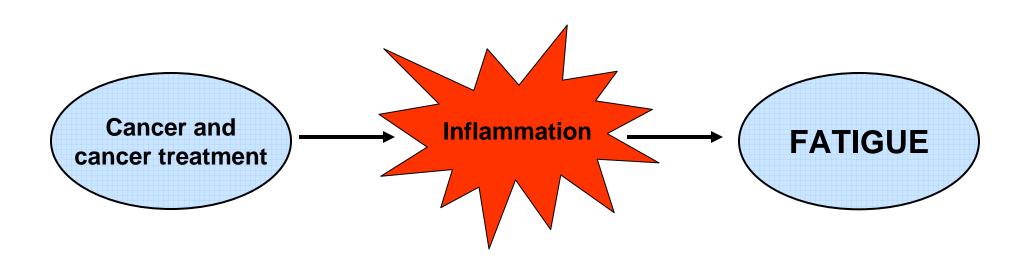
Inflammation

- Body's response to infection or injury
- Mediated by proinflammatory cytokines
 - IL-1 β , IL-6, TNF- α
- Local and systemic effects, including effects on CNS

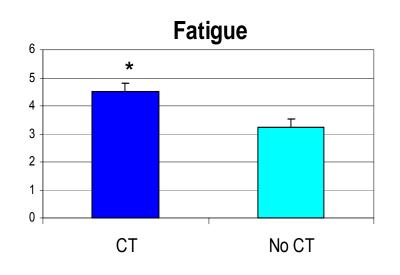


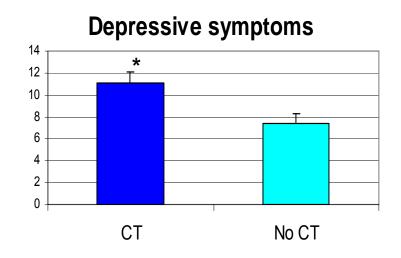


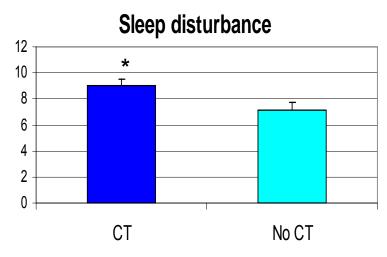
Model of cancer-related fatigue



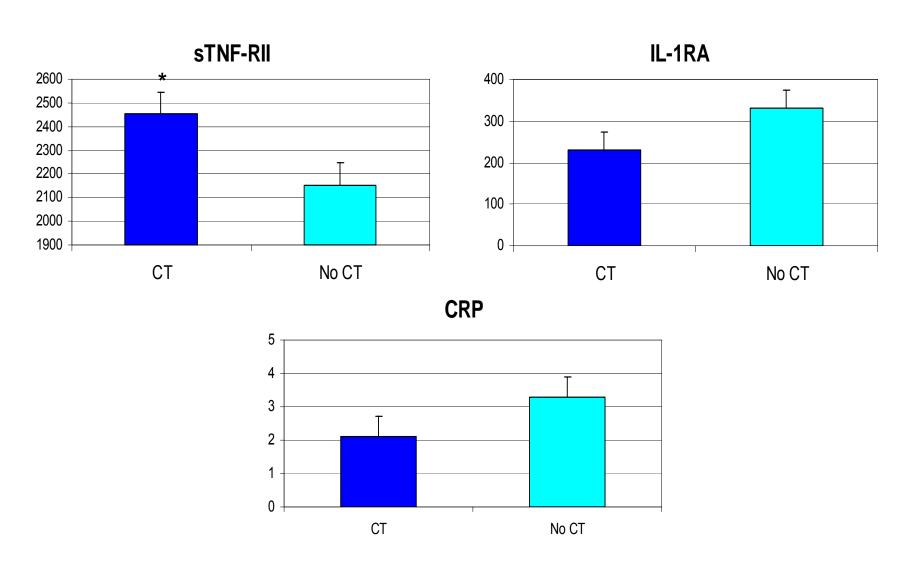
Acute effects of chemotherapy on fatigue and other symptoms



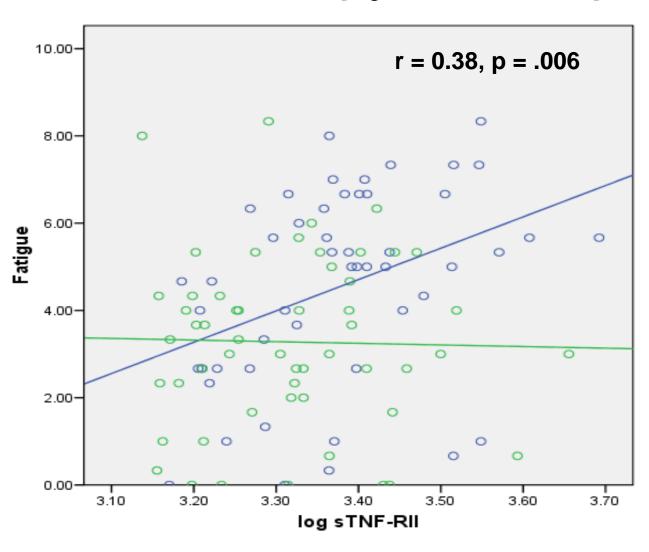


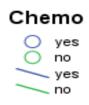


Acute effects of chemotherapy on inflammatory markers



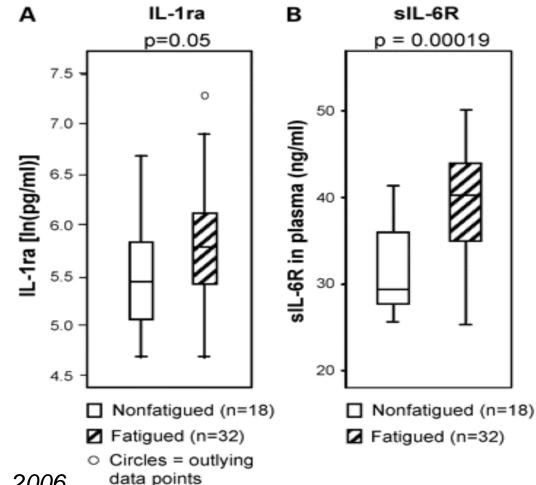
Fatigue correlated with sTNF-RII in chemotherapy treated patients





Elevations in inflammatory markers in fatigued BCS 1-5 years post-dx

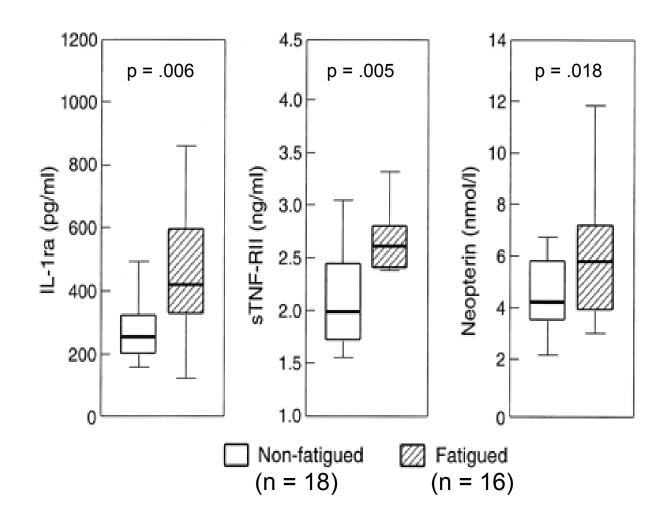
Fatigued
 BCS show
 elevations in
 IL-1 receptor
 antagonist
 and soluble
 IL-6 receptor
 relative to
 non-fatigued
 survivors



Collado-Hidalgo, Bower et al., 2006

Elevations in inflammatory markers in fatigued BCS 3-7 years post-dx

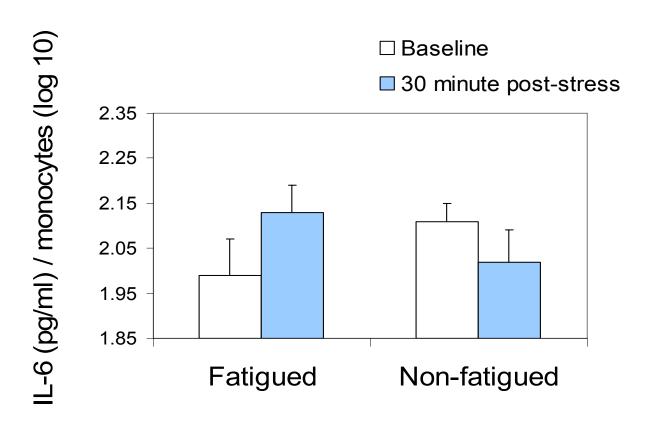
Fatigued
 BCS show
 elevations in
 IL-1 receptor
 antagonist,
 soluble TNF
 receptor II,
 and
 neopterin



Bower et al., 2002

Elevations in cytokine production following psychosocial stress

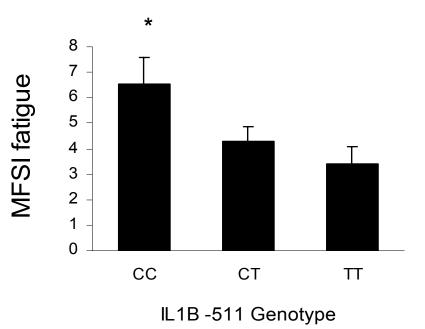
Elevated
 cytokine
 production
 after speech +
 math stressor
 in fatigued
 BCS



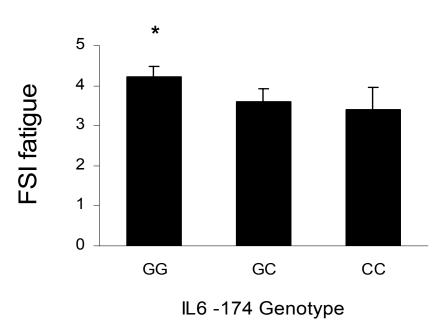
Cytokine gene polymorphisms

- Focus on SNPs in promoter regions of genes that encode proinflammatory cytokines
 - IL1B -511
 - IL6 174

 IL1B-511: elevated fatigue in CC group



 IL6-174: elevated fatigue in GG group



Treating fatigue

How can we treat cancer-related fatigue?

- If possible, identify and treat underlying factors
 - Depression
 - Physical symptoms (sleep disturbance, pain)
 - Anemia
 - Medical conditions

Non-specific interventions

- Pharmacologic
 - Antidepressants
 - Psychostimulants
- Behavioral/Psychological
 - Psychosocial
 - Exercise
 - Complementary and alternative medicine

Pharmacologic interventions

- Antidepressants
 - Meta-analysis of RCTs shows no effect of paroxetine

	Antid	PI	Placebo			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Morrow 2003	-4.8	21.3	277	-3.4	20.3	272	85.5%	-0.07 [-0.23, 0.10]	-∭ -
Roscoe 2005	-5	6.6	44	-2.5	17.8	50	14.5%	-0.18 [-0.59, 0.23]	
Total (95% CI)			321			322	100.0%	-0.08 [-0.24, 0.07]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.25, df = 1 (P = 0.61); l ² = 0%									1 05 0 05 1
Test for overall effect: Z = 1.06 (P = 0.29)									-1 -0.5 0 0.5 1 Favors treatment Favors control

Pharmacologic interventions

- Psychostimulants
 - Meta-analysis of RCTs shows reduction in fatigue with methylphenidate

	Psych	Placebo				Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Bruera 2006	-9.6	9.8	56	-7.5	11.3	56	42.7%	-0.20 [-0.57, 0.17]	
Fleishman 2005	-11.8	12.6	75	-7.1	12.6	77	57.3%	-0.37 [-0.69, -0.05]	
Total (95% CI)			131			133	100.0%	-0.30 [-0.54, -0.05]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.48, df = 1 (P = 0.49); I ² = 0%									
Test for overall effect: Z = 2.40 (P = 0.02)								-1 -0.5 0 0.5 1 Favors treatment Favors control	

Pharmacologic interventions

- Psychostimulants
 - Recent interest in modafinil (Provigil) developed for treatment of narcolepy
 - Preliminary data from uncontrolled trials suggests beneficial effects on fatigue (Blackhall et al., 2009)
 - Recent RCT indicates beneficial effects among patients undergoing CT with severe fatigue (Jean-Pierre et al., 2010)

Novel pharmacologics

- Anti-cytokine therapies
 - Medications that block proinflammatory cytokines have been approved for certain inflammatory conditions (e.g., rheumatoid arthritis, psoriasis)
 - These medications are effective in reducing fatigue associated with these conditions
 - Preliminary data suggests beneficial effect on fatigue in cancer populations (Monk et al., 2006)

Psychological interventions

- Primarily designed to provide information, reduce stress, improve coping, and increase social support
- Also have beneficial effects on fatigue (Jacobsen et al., 2007; Kangas et al., 2008)

Moving Beyond Cancer psychoeductional intervention

- Video designed to promote realistic expectations and model active coping led to improvements in fatigue among women completing treatment for early stage breast cancer (Stanton et al., 2005)
- Beginning of video showed a woman walking up a hill (modeling physical activity) and getting help with chores

Cognitive Behavioral Therapy for severe cancer-related fatigue

- Individual therapy sessions led to improvements in fatigue among fatigued cancer survivors (Gielissen et al., 2006)
- Sessions addressed factors thought to perpetuate fatigue
 - Fears about recurrence, maladaptive coping (catastrophizing), dysregulated sleep and activity patterns, poor social support

Exercise interventions

- Patients that exercise during treatment report lower levels of fatigue
- Exercise interventions also show beneficial effects on fatigue during and particularly after treatment
 - Lab-based exercise programs
 - Home-based walking

Information and pedometer

- Breast cancer survivors who received information about exercise and a step pedometer showed reduced fatigue (Vallence et al., 2007)
 - Also showed increases in self-reported physical activity and QOL

Complementary and Alternative Medicine (CAM) interventions

- Many cancer patients and survivors use CAM therapies
 - Acupuncture
 - Tai Chi, Qigong
 - Energy therapies
 - Yoga

Yoga for cancer-related fatigue

- Yoga incorporates active components of interventions with beneficial effects on fatigue
 - Exercise
 - Stress management/relaxation
- Adaptable for fatigued patients who may not be able to participate in standard exercise programs

Intervention format

- 12 weeks, two 90-minute classes per week
- Based on teachings of B.K.S. Iyengar
- Focus on poses thought to be effective for reducing fatigue
 - Passive backbends
 - Passive inversions
- Specific sequencing of poses, moving from easier to more challenging

Key poses: passive backbends

Setubandha Sarvangasana, Full bridge Posture, on crossed bolsters and blankets



Key poses: passive backbends

Setubandha Sarvangasana, Full bridge Posture, on crossed bolsters and blankets





Key poses: passive inversions

Salamba Sarvangasana, Supported Shoulderstand, with a chair, bolster, mat, and blanket

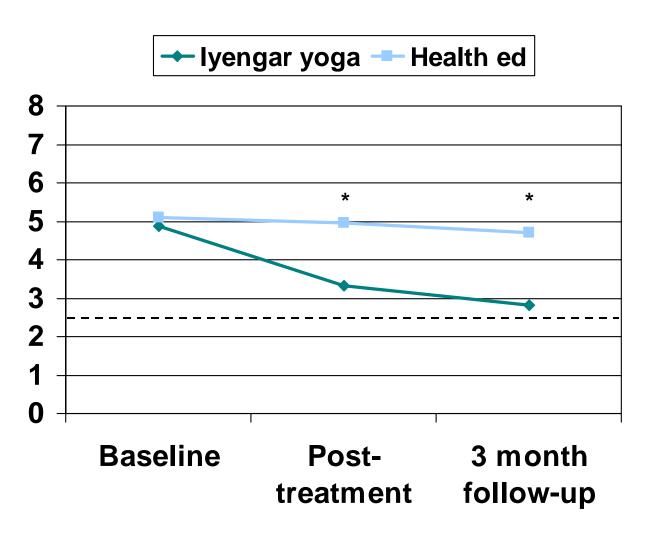


Key poses: restorative

Supta Baddhakonasana, Reclining bound angle posture, with bolster, strap, and blankets

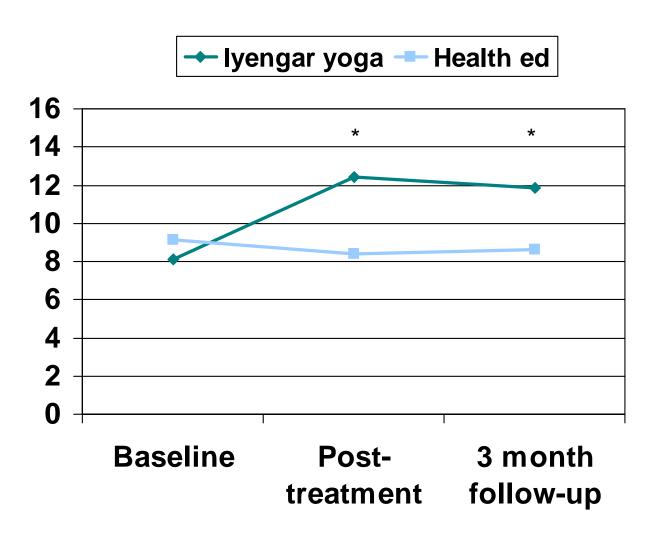


Yoga reduces fatigue



Group x time interaction: F(2, 54) = 3.99, p = .024

...and increases vigor



Group x time interaction: F(2, 54) = 6.67, p = .003

Quotes from participants

"The physical and mental changes are subtle, but I feel like I'm thinking more clearly, have less brain fog, have more energy, fatigue later rather than sooner, feel better in general, feel stronger."

"(The) effects of yoga have been small each week but the cumulative effect has been noticeable. I know that it is ameliorating the fatigue...There's been enough progress, subtle and incremental, to believe I can get much better."

General recommendations for preventing and treating fatigue

- Address underlying issues depression, medical problems
- Get moving incorporate regular physical activity into your life
- Challenge negative thoughts and beliefs about fatigue
- Consider more targeted intervention cognitive/behavioral, yoga

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