

# **DISTURBI COMPLESSI: IL PARADIGMA DELLA FATIGUE**

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# CRF: DEFINITION (ASCO, NCCN, ESMO)

## Cancer-related fatigue




a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment, not proportional to recent activity, interfering with usual functioning and

**NOT alleviated by rest or sleep**

# CRF: INCIDENCE - PREVALENCE

Supportive Care in Cancer  
<https://doi.org/10.1007/s00520-018-4399-9>

ORIGINAL ARTICLE

 CrossMark

Prevalence, characteristics, and treatment of fatigue in oncological cancer patients in Italy: a cross-sectional study of the Italian Network for Supportive Care in Cancer (NICSO)

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CRF is reported by 60-65% of patients

CRF can occur any time in cancer patients

- **up to 40% of patients report fatigue at diagnosis**
- **80% and 90% of patients during chemotherapy and radiotherapy**
- **30%-35% of patients in the post-treatment phase**

## THE STUDY

- A cross-sectional study evaluating fatigue in 1394 cancer patients attending for any reason the 24 Italian participating centers.

# RESULTS

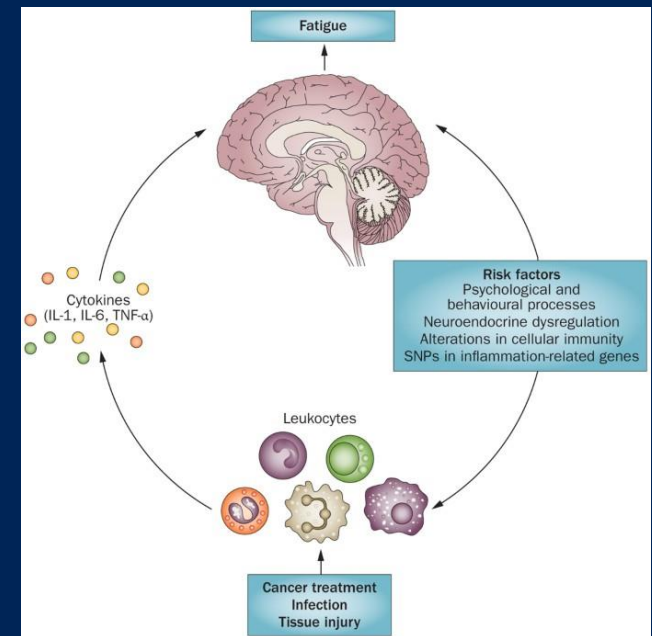
- CRF was referred by **62.1%** of patients, a value similar to the literature data.
- CRF may arise at any time in oncological patients: by 49.7% of patient survivors, by 81.2% of patients receiving supportive care and by about 62.1%-66.9% of patients in active treatment.

## RESULTS

- The intensity of CRF was moderate/severe in 43% / 29.2% of patients and the duration was > 4 months in 50.9% of patients.
- The majority of patients presented CRF interfering with quality of life.

# CRF: ETIOLOGY

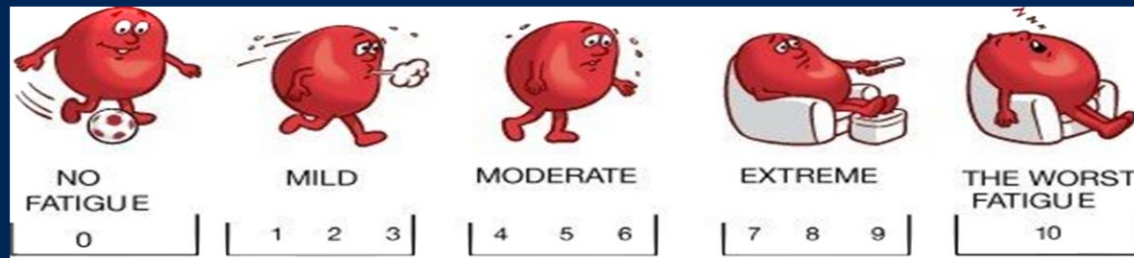
- The mechanisms responsible for CRF are poorly understood
- Possible causes of CRF are:
  - direct CNS toxicity of cancer treatment
  - neurophysiologic skeletal muscle changes (so-called vagal afferent activation)
  - systemic inflammatory response
  - loss of muscle mass, defective muscle energy metabolism or abnormalities in the use of ATP
  - hypothalamic-pituitary-adrenal axis dysfunction
  - disrupted sleep or circadian rhythms
  - production of proinflammatory cytokines



*Ryan JL, et al. The Oncologist 2007;12(suppl 1):22–34*  
*Bauer JE, et al. Nature Reviews Clinical Oncology 2014;: 597-609*

# CRF: SCREENING AND DIAGNOSIS

- All cancer patients should be routinely screened for the presence and severity of fatigue at their first visit, and then during therapy and approximately every year during the post-treatment phase
- Screening should be done using brief and validated tools with established cut-off values for severity (e.g., Numerical Rating Scale)





## THE BRIEF FATIGUE INVENTORY

reliable and easily understood questionnaire, validated in many languages

Brief Fatigue Inventory										
STUDY ID# _____					HOSPITAL # _____					
Date: ____/____/____					Time: _____					
Name _____			_____			_____		_____		
Last			First			Middle Initial				
Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes <input type="checkbox"/> No <input type="checkbox"/>										
1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.										
0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine
2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.										
0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine
3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.										
0	1	2	3	4	5	6	7	8	9	10
No										As bad as
Fatigue										you can imagine
4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:										
<b>A. General activity</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
<b>B. Mood</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
<b>C. Walking ability</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
<b>D. Normal work (includes both work outside the home and daily chores)</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
<b>E. Relations with other people</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes
<b>F. Enjoyment of life</b>										
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely Interferes

# CRF: SCREENING AND DIAGNOSIS

In patients who test positive for CRF (score  $\geq 4$ , indicating moderate to severe fatigue) the factors that contribute to CRF should be identified and, whenever possible, treated

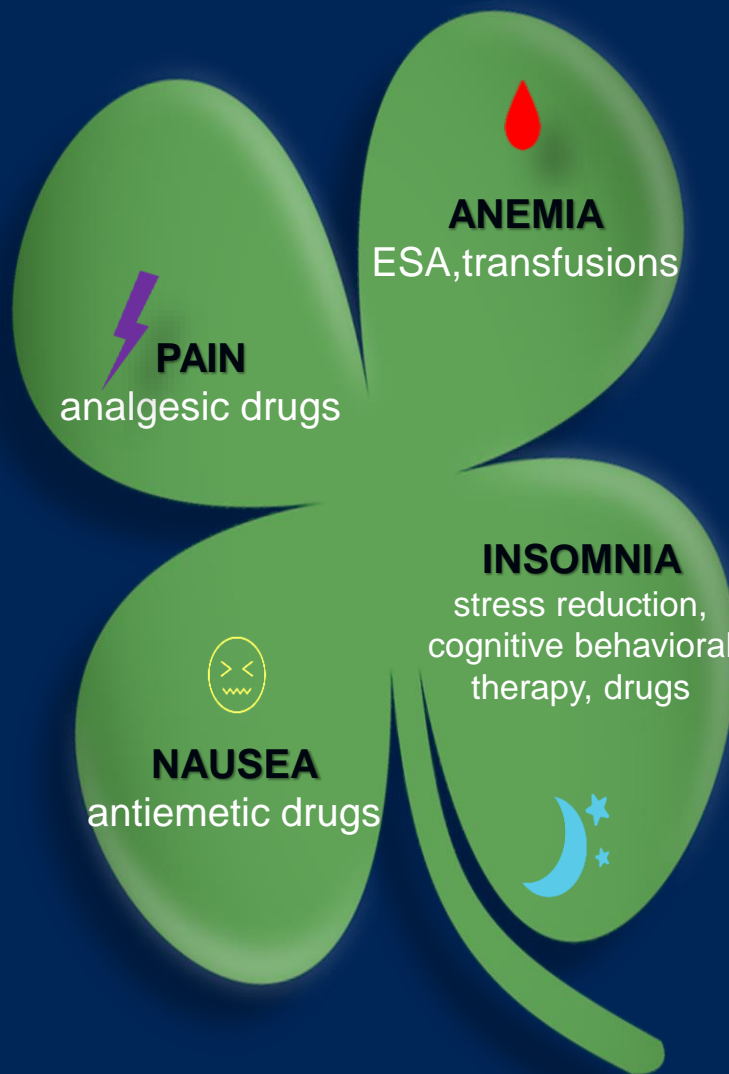




# CRF: CONTRIBUTING FACTORS

<b>HEMATOLOGICAL ALTERATIONS</b>	Anemia
<b>NUTRITIONAL AND FLUID IMBALANCES</b>	Weight loss, changes in caloric intake, fluid and electrolyte imbalances, gastrointestinal tract motility disorders
<b>CANCER THERAPY</b>	Chemotherapy, radiotherapy, surgery, immunotherapy, hormone therapy, molecularly targeted agents
<b>MEDICAL COMORBIDITIES</b>	Endocrinopathies (hypothyroidism, hypogonadism, diabetes mellitus), cardiopulmonary disorders, hepatic, renal and neurological dysfunctions, adrenal insufficiency, infections
<b>SYMPTOM BURDEN</b>	Pain, anxiety, depression, dyspnoea, sleep dysfunction, nausea
<b>MEDICATIONS</b>	Opioids, sedating agents (hypnotics, neuropathic agents, antihistamines), beta blockers

# CRF: TREATMENT OF CONTRIBUTING FACTORS



**Physical Examination**



**Status of the  
Underlying  
Malignant Disease**



**COMPREHENSIVE AND  
FOCUSED  
SCREENING AND  
DIAGNOSIS**



**Review  
of body systems**



**Fatigue History**



**Laboratory Tests**

Electrolytes  
Chemistry panel  
Thyroid-stimulating hormone  
Complete blood count  
Serum testosterone



**Psychological  
Status Examination**



## CRF : TREATMENT

If patients refer mild fatigue (score  $\leq 3$ , not interfering with activities of daily living) patients can be reassured and counseled about strategies for coping with fatigue



# PHARMACOLOGICAL INTERVENTIONS

# PHYTOPHARMACEUTICALS NUTRICEUTICALS

PSYCHOSTIMULANTS

ANTIDEPRESSANTS

ACETHYLCHOLINE INHIBITORS

CORTICOSTEROIDS

ESZOPICLONE

MEGESTROL ACETATE



WISCONSIN GINSENG

ASIAN GINSENG

GUARANA

MISTLETOE

ASTRAGALUS

L-CARNITINE

COENZIME Q10

MELATONIN

TAURINE

# NON-PHARMACOLOGICAL INTERVENTIONS

PHYSICAL EXERCISE

PSYCHOSOCIAL INTERVENTIONS

MIND-BODY INTERVENTIONS

# PHARMACOLOGICAL INTERVENTIONS

- Several randomized, double-blind, placebo-controlled studies have been carried out
- At the present time, no treatment has been approved by the US FDA for the management of CRF





# PSYCHOSTIMULANTS - Phase II-III RCTs

DRUG	AUTHOR	NUMBER OF PATIENTS	RESULTS
<b>Dexmethylphenidate, Methylphenidate</b>	Lower, 2009	154	Positive
	Mar Fan, 2008	57	Negative
	Butler, 2007	68	Negative
	Bruera, 2006	112	Negative
	Moraska, 2010	148	Negative
	Roth, 2010	32	Positive
	Escalante, 2014	38	Negative
	Richard, 2015	24	Negative
	Bruera, 2013	141	Negative
	Mitchell, 2015	43	Negative
	Kerr, 2012	30	Positive
Hanna, 2006	37	Positive	
<b>Modafinil</b>	Jean-Pierre, 2010	867	Negative
	Boele, 2013	37	Negative
	Spathis, 2014	208	Negative
	Hovey, 2014	83	Negative
<b>Armodafinil</b>	Berenson, 2015	50	Negative
	Page, 2015	54	Negative
	Lee, 2016	81	Negative
	Heckler, 2016	96	Negative
<b>Dexamphetamine</b>	Auret, 2009	50	Negative

## PSYCHOSTIMULANTS

- A subgroup analysis suggested some benefit in the control of severe fatigue in 2 trials (1 with methylphenidate and 1 with modafinil).
- In several trials the study was interrupted before reaching the determined sample size (10 of the 21 studies) often for refusal of pts to participate in the study.
- A loss of enrolled pts after randomization of more than 15% was shown in 12 of the 21 studies.

# PSYCHOSTIMULANTS: CONCLUSIONS

- Therefore, more well planned studies with a larger number of pts are necessary to define the role of psychostimulants in cancer-related fatigue.
- These studies should always be placebo-controlled studies; in fatigue control, the placebo has an important role.

# OTHER DRUGS - Phase II-III RCTs

DRUG	AUTHOR	NUMBER OF PATIENTS	RESULTS
<b>ANTIDEPRESSANT</b>			
<b>Paroxetine</b>	Morrow, 2003	704	Negative
	Roscoe, 2005	94	Negative
<b>Sertraline</b>	Stockler, 2007	189	Negative
<b>ACETHYLCHOLINESTERASE INHIBITORS</b>			
<b>Donepezil</b>	Bruera, 2007	142	Negative
<b>SEDATIVE HYPNOTIC DRUG</b>			
<b>Eszopiclone</b>	Dimsadale, 2011		Negative
<b>CORTICOSTEROIDS</b>			
<b>Dexamethasone</b>	Yennurajalingam, 2013	132	<b>Positive</b>
	Paulsen, 2014	50	<b>Positive</b>
<b>Methylprednisolone</b>			
<b>PROGESTINIC AGENT</b>			
<b>Megestrol acetate</b>	Bruera, 1998	53	Negative

**steroids significantly reduced CRF in terminal cancer pts**

# CORTICOSTEROIDS

(Yennurajalingam S, J Clin Oncol 2013; 31: 3076-82)

- A double-blind randomized study comparing dexamethasone (4 mg bid for 14 days) versus placebo in 84 terminal cancer pts with fatigue  $\geq 4$  has been carried out.
- Dexamethasone significantly reduced fatigue and ameliorated quality of life (physical symptoms)
- Adverse events were not significantly different

# CORTICOSTEROIDS

(Pauling O, et al, J Clin Oncol 2014; 32: 3221-28)

- Another study evaluated the effects of methylprednisolone 16 mg bid versus placebo administered for 7 days on pain, fatigue and appetite loss, in 50 patients with advanced cancer. Primary endpoint: average pain intensity after 7 days. Fatigue was a secondary endpoint.
- Patients receiving methylprednisolone did not experience an improvement of cancer pain but fatigue, appetite loss and pt satisfaction was ameliorated with respect to placebo.
- Long-term steroid use should be avoided due to the possible side effects.

# PHARMACOLOGIC TREATMENT: CONCLUSIONS

- All studied drugs for cancer-related fatigue, with the exception of dexamethasone and methylprednisolone in terminal cancer pts, obtained negative results.
- It is necessary to better identify neuroreceptors involved in fatigue (to personalize therapy).
- It is necessary to study more selected pt populations (e.g., pts with moderate-severe or only severe fatigue; pts submitted to CT, or to RT, or terminal cancer pts).

# PHYTOPHARMACEUTICALS - NUTRICEUTICALS

**WISCONSIN GINSENG**

**ASIAN GINSENG**

**GUARANA**

**MISTLETOE**

**ASTRAGALUS**

**L-CARNITINE**

**COENZIME Q10**

**MELATONIN**

**TAURINE**



# WISCONSIN GINSENG

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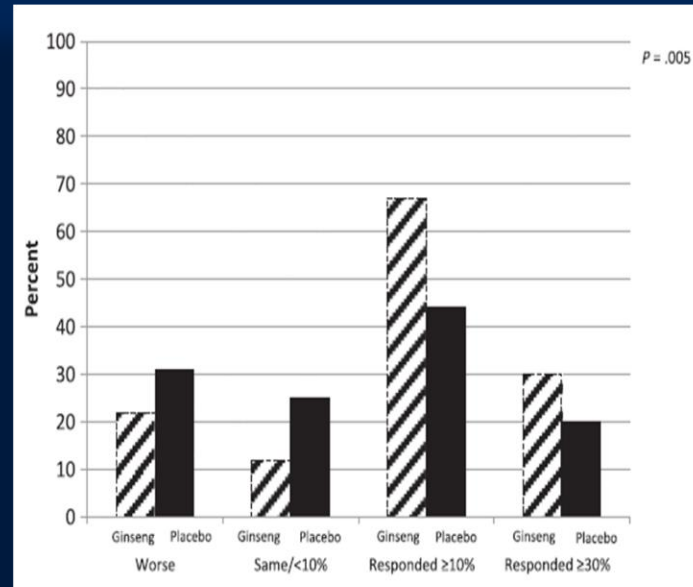
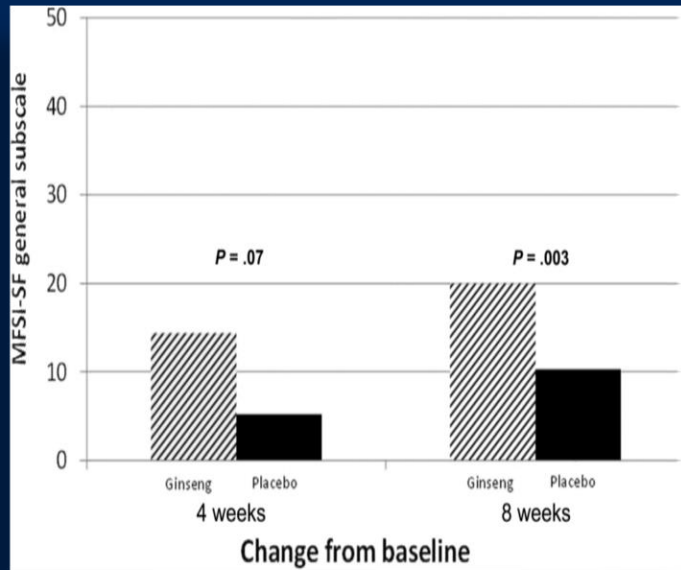
## ARTICLE

### Wisconsin Ginseng (*Panax quinquefolius*) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2

Debra L. Barton, Heshan Liu, Shaker R. Dakhil, Breanna Linquist, Jeff A. Sloan, Craig R. Nichols, Travis W. McGinn, Philip J. Stella, Grant R. Seeger, Amit Sood, Charles L. Loprinzi

Manuscript received December 21, 2012; revised March 18, 2013; accepted June 13, 2013.

- A double-blind trial randomized 364 fatigued cancer patients undergoing or having completed curative treatment to 2000 mg of American ginseng vs placebo (two doses a day) for 8 weeks



# WISCONSIN GINSENG

(Barton D et al. JNCI 2013; 105: 1230-38)

- A statistically significant difference was seen at 8 weeks with a change score from baseline of 20 for the ginseng group and 10.3 for the placebo (Multidimensional Fatigue Symptom Inventory). The difference was not significant at 4 weeks. Toxicity did not differ significantly between the two arms.
- The study included a heterogeneous population (different neoplasms and stages of disease). More studies are needed to identify the role of Wisconsin ginseng.

# **ASIAN (KOREAN) RED GINSENG**

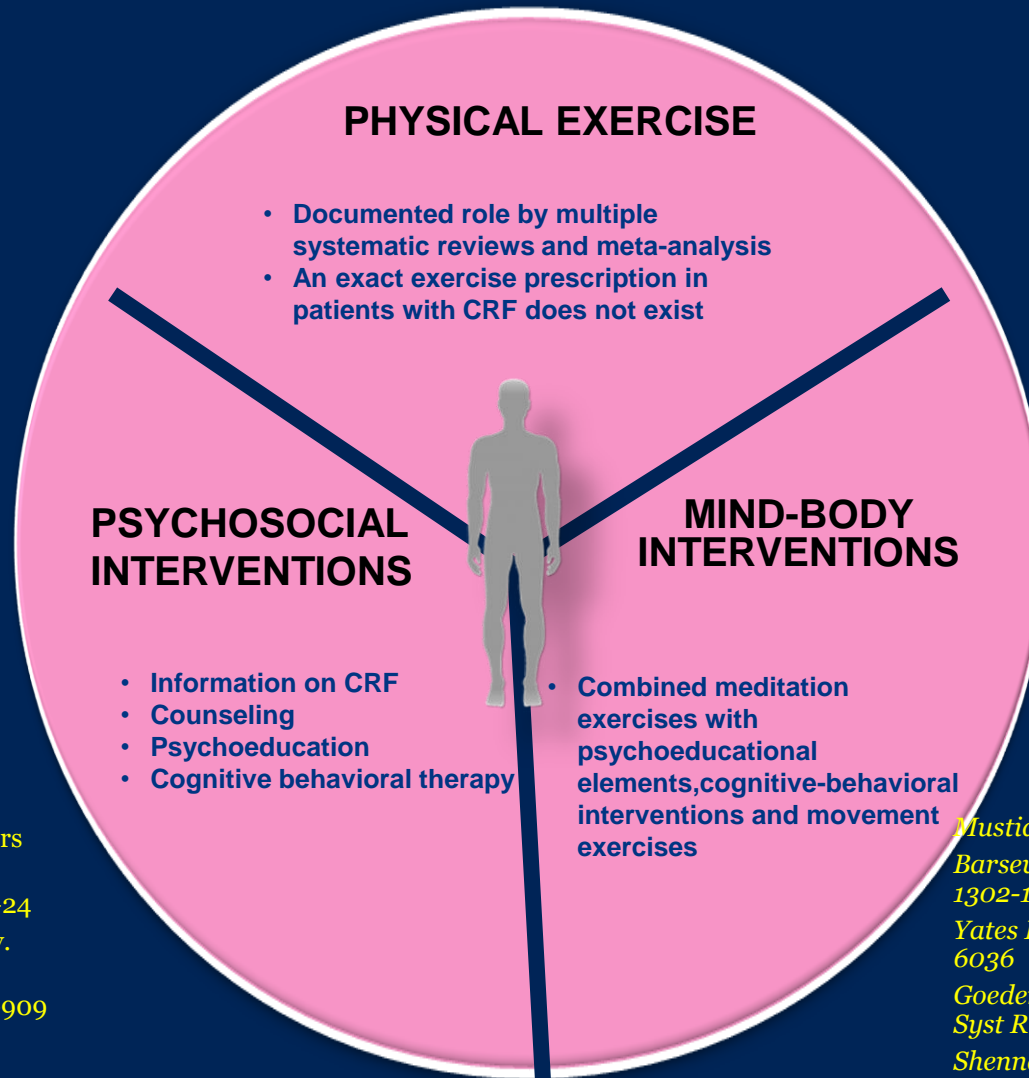
**(Kim JW et al. Eur J Cancer 2020; ; 130: 51-62)**

- A double-blind trial randomized 438 fatigued cancer patients receiving oxaliplatin-containing chemotherapy, either in adjuvant or metastatic disease setting, to 2000 mg of Korean red ginseng vs placebo (two doses a day) for 16 weeks.
- At 16 weeks Korean red ginseng improved CRF compared to placebo; but the differences were significant only in «mood» and «walking ability» Toxicity did not differ significantly between the two arms but neutropenia was more frequent with ginseng (19% vs 10%).

# PHYTOPHARMACEUTICAL AND NUTRICEUTICAL INTERVENTIONS: CONCLUSIONS

- More studies are requested to define if these interventions could have a role in the treatment (or perhaps in the prevention) of CRF
- These studies should be methodologically well done to answer a defined question on efficacy of phytopharmaceuticals and nutraceuticals

# NON-PHARMACOLOGICAL INTERVENTIONS



Brown JC, Cancer Epidemiol Biomarkers Prev. 2011;20:123-133

Puetz Tw, Am J Prev Med 2012; 43:e1-24

Mishra SI, Cochrane Database Syst Rev. 2012;15(8):CD007566

Galvao DA, J Clin Oncol 2005;23:899-909

Courneya KS, J Natl Cancer Inst. 2013;105:1821-1832

Mustian K, Oncologist 2007; 12: 52-67

Barsevick AM, Cancer 2004; 100: 1302-1310

Yates P, J Clin Oncol 2005; 23: 6027-6036

Goedendorp MM, Cochrane Database Syst Rev 2009: CD006953

Shennan C, Psychooncology 2011; 20: 681-697

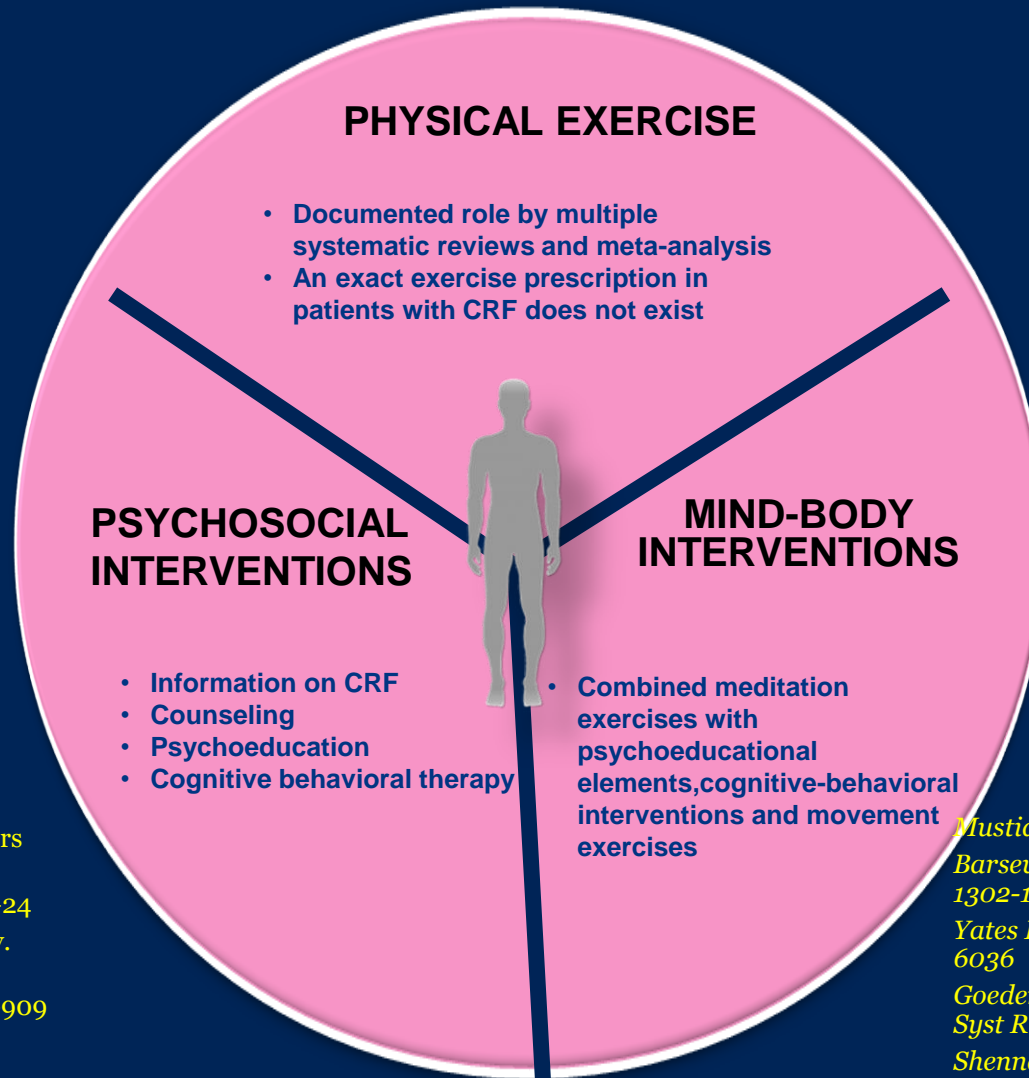
# PHYSICAL EXERCISE

- Common barriers to physical activity in cancer survivors include physical and disease-related limitations (e.g., pain, weakness) as well as lack of time, lack of interest/motivation, lack of facilities and lack of encouragement from family.

# EXAMPLES OF ENERGY PRESERVATION

- alternate tasks that take lots of energy with those that take less
- plan activities daily as well as weekly to better alternate tasks
- delegate as much as possible
- arrange your household so that most activities can be done on one floor
- balance activities so that you alternate resting and doing
- sit to do things whenever possible
- use assistive device: walkers, scooters, canes, handrail...
- wash your hair in the shower rather than over a sink
- - use a terry robe instead of towels to dry off
- wear loose clothes that are easier to put on and take off
- .....

# NON-PHARMACOLOGICAL INTERVENTIONS



Brown JC, Cancer Epidemiol Biomarkers Prev. 2011;20:123-133

Puetz Tw, Am J Prev Med 2012; 43:e1-24

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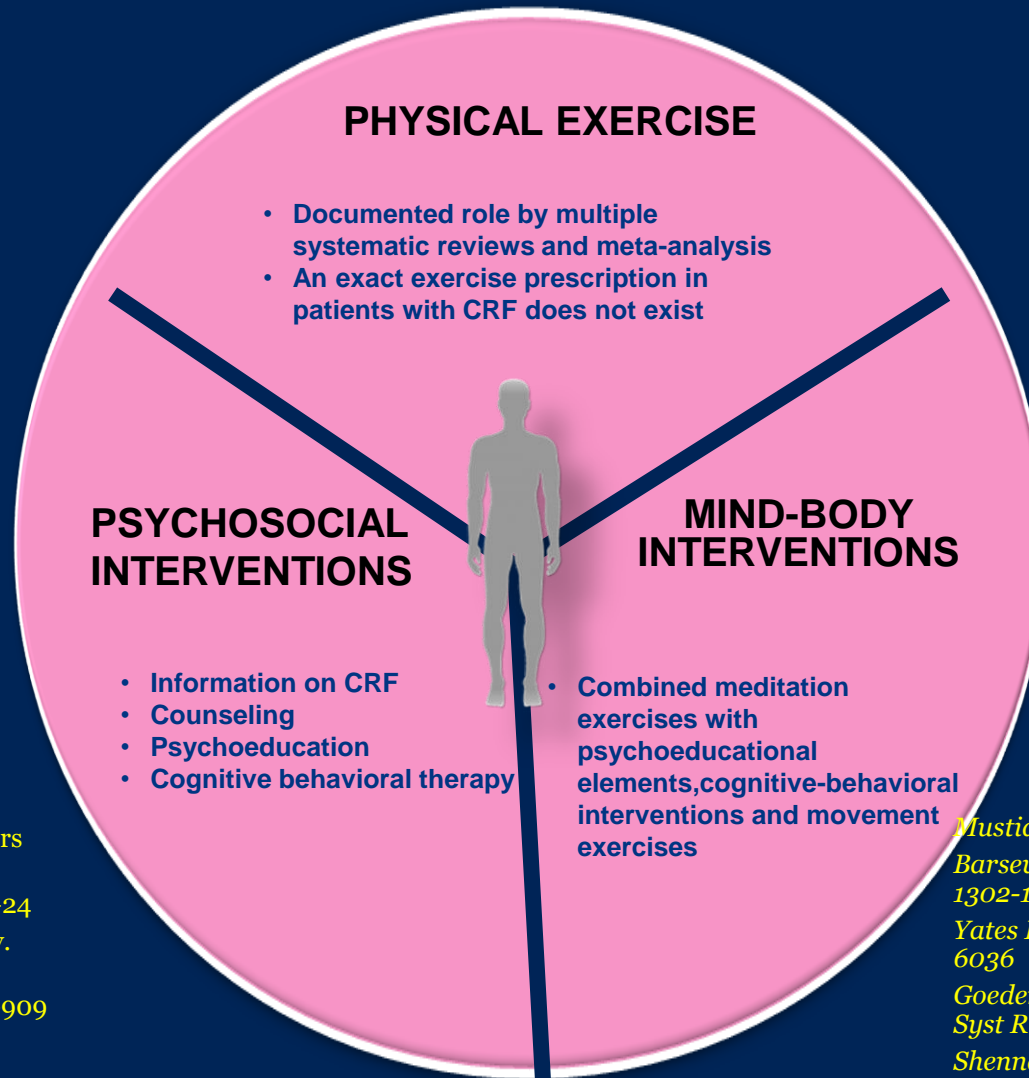
Shennan C, Psychooncology 2011; 20: 681-697



# PSYCHOSOCIAL TREATMENT

- Cognitive behavioral therapy is generally used to address the following factors: coping with the experience of cancer; fear of disease recurrence; dysfunctional thoughts and beliefs regarding fatigue, sleep dysregulation, etc.

# NON-PHARMACOLOGICAL INTERVENTIONS



Brown JC, Cancer Epidemiol Biomarkers Prev. 2011;20:123-133

Puetz Tw, Am J Prev Med 2012; 43:e1-24

Mishra SI, Cochrane Database Syst Rev. 2012;15(8):CD007566

Galvao DA, J Clin Oncol 2005;23:899-909

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Shennan C, Psychooncology 2011; 20: 681-697

# MIND-BODY INTERVENTIONS

The following interventions may offer some benefit:

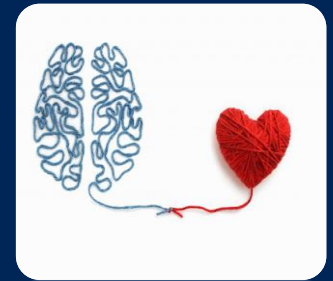
- Mindfulness-based stress reduction

*(Grenlee H, J Natl Cancer Inst Monogr. 2014; 50: 346-358)*

- YOGA

- ACUPUNCTURE

- **OTHER:** Biofield therapies (touch therapy), Massage, Music therapy, Relaxation, Moxibustion (applications of heat of burning herbs on the skin), Reiki, Qigong (traditional Chinese energy exercises and therapies)



# MIND-BODY INTERVENTION: YOGA



- A combination of physical poses with a focus on breathing and meditation
- CRF reduction demonstrated by
  - a Cochrane review evaluating 24 studies in breast cancer patients
  - a systematic review including 29 randomized controlled trials
  - a randomized clinical trial in 410 cancer survivors

*Danhauer SC, Cancer 2019; 125: 1979-89*  
*Cramer H, Cochrane Database Syst Rev*  
*2017; 3: 1*  
*Po-Ju L, Integr Cancer Ther 2019; 18:*  
*1534735419855134*

# MIND-BODY INTERVENTIONS: ACUPUNCTURE

- Several randomized controlled trials have been carried out in order to evaluate acupuncture
- A meta-analysis of 10 randomized clinical trials including 1327 patients who have completed cancer treatment showed that acupuncture reduced CRF



Zeng Y, *Integr Cancer Ther* 2014; 13: 193-200  
Zhang Y, *Support Care Cancer* 2018; 26: 415-425

# TAKE HOME MESSAGES



1. **THINK** about CRF (one of the most frequent and distressing adverse events of antineoplastic treatments)
2. **SCREEN** all cancer patients routinely for CRF
3. **IDENTIFY** and possibly **TREAT** the contributing factors in case of CRF  $\geq 4$  on the NRS
4. **CONSIDER** CRF treatments

