

# Physical Long-Term and Late Effects

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# FIRST

Most cancer survivors (60-80%?)  
5+ years after treatment have good-  
excellent health by self-report.

1 in 5 will continue to have impairments that  
impact work-related function. (NCI report)

# NEXT

Physical impairments DO have major impact  
on function and quality of life in a  
meaningful minority of cancer survivors.

# IT DEPENDS

Risks for long term or late physical effects vary by:

Disease

Type of treatment

Age at treatment

Time since treatment

Genetic vulnerability

Etc...

# FURTHER

Physical impairments vary by organ system. They may have major impact on an aspect of quality of life for a majority, while not being evident in overall physical function (sexuality).

# Physical Limitations in Survivors

## Population-Based, Case-control studies:

- Adult long term survivors vs non-survivors in the NHANES cohort (*Ness et al, Ann Epi, 16, 2006*)
  - ✓ Physical limits 53% vs 21%
  - ✓ Restricted participation in activities 31% vs 13%
- Childhood cancer survivors 5 yrs + vs siblings have increased functional and physical limitations (*Robison, Oeffinger, Ness et al, numerous studies; Maunsell et al several studies*)
  - ✓ Restricted participation in activities, work, school, personal care skills
  - ✓ Good-excellent health reported by 62% vs 71%.
  - ✓ CNS and bone cancers had greatest increased risk of poor health.
- **Elderly women** (*Sweeney et al, JNCI, 98, 2006*)
  - ✓ Modest % differences: 42% vs 31% heavy housework, 26% vs 19% unable to walk a half mile.
  - ✓ No difference in symptoms or chronic conditions between survivors and controls. Survivors and controls attributed problems to aging not cancer. (*Heidrich et al, Onc Nurs Forum, 33, 2006*)

# Physical Limitations in Survivors

## Population-based or large, case-control studies of specific diseases:

- Breast cancer survivors have increased physical impairment and symptoms depending on treatment (*Ganz, Rowland et al, several*)
- Prostate cancer: increased fatigue regardless of type of treatment, urinary symptoms, sexual dysfunction (though few seek treatment)
- Testicular cancer: slight if any differences from controls in most physical domains (vitality lower) (*Mykletun et al. JCO, 23, 2005*)
- Hematopoietic stem cell transplant (HSCT) physical limits and increased comorbidities (*Andrykowski, Wingard et al, Bhatia, Baker, et al, Syrjala et al*)

# Other Physical Limitations in Survivors

## Higher rate of specific deficits than controls:

- Cardiovascular diseases
- Thyroid dysfunction (majority hypothyroid)
  - ✓ Thyroid levels may be within normal range after HSCT but 40% of males and 54% of females over-responded to TRH stimulation, suggesting subclinical hypothyroidism. (*Somali et al, 37, 2005*)
  - ✓ Thyroid deficits may have late onset, 3 years or later after HSCT. (*Berger et al, BMT, 35, 2005*)
- Pulmonary function
- Osteoporosis / bone loss
- Dental impairments
- Cataracts
- Hearing and vision loss
  - ✓ Infrequent
  - ✓ Hearing loss most common after head and neck cancer, sarcomas, testicular cancers, cisplatin treatment. (*Stava, 2005*)

# Other Physical Limitations in Survivors

Do long term survivors **maintain or decline over time?**

➤ Answer not clear yet.

- ✓ Most studies are cross-sectional case-control.
- ✓ Differences in case incidence over time may be due to changes in treatment or other changing risk factors.
  - Example: Longest survivors of HSCT received single dose total body irradiation (TBI)
  - Sub-groups have higher rates of complications
  - Treatment is no longer used
  - New treatments are used with unknown long term effects; new diseases are treated
  - **Longitudinal studies are needed.**

# HSCT Long Term Survivor Cohorts

(RFA: CA78990)

**DESIGN: 2 prospective longitudinal transplant survivor cohorts:**

▶ **10 Year: 7 time points, N=405, 137 @ 10 yrs:**

■ Pretx, active treatment, 3mo and 1, 3, 5, 10 years

▶ **5 Year: 7 time points, N=199, 98 @ 5 yrs:**

■ Pretx, discharge (3mo), 6mo, 1, 2, 3 and 5 years

▶ **Case-Matched Controls**

■ 10 year cohort: at 10 year assessment

■ 5 year cohort: at 5 year assessment

10 Year Survivors after Transplant  
(N=137 with case matched controls)  
**Sum of Medical Problems**

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	<b>Survivors</b>	<b>Controls</b>	<b><i>P</i></b>
<b># of 85 possible active diseases or symptoms</b>			
<b>Mean (SD)</b>	<b>5.9 (SD 6.8)</b>	<b>3.4 (SD 4.0)</b>	<b>&lt;.001</b>
<b>Median</b>	<b>4</b>	<b>2</b>	

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# 10 Year Survivors after Transplant (N=137) Prevalence of Medical Problems

Syrjala et al, *JCO*, 2005, 23:6596

	<b>Survivors</b>	<b>Controls</b>	<b>P</b>
<b><u>History of cataract surgery</u></b>	<b>51 (38%)</b>	<b>1 ( 1%)</b>	<b>&lt;.001</b>
High blood pressure	29 (21)	16 (12)	.09
<u>2<sup>nd</sup> cancer</u> (not recurrence) in 10 yrs	15 (11)	9 ( 7)	.41
Basal or squamous cell cancer	8 ( 6)	4 ( 3)	.39
Other malignancy	8 ( 6)	6 ( 4)	.99
<u>Thyroid disease</u>	10 ( 7)	6 ( 4)	.45
Diabetes (in past 10 yrs)	7 ( 5)	2 ( 2)	.29
Pulmonary disease	2 ( 2)	0	.50
<u>Osteoporosis</u>			
Women (n = 71)	3 ( 4)	2 ( 3)	1.0
Men (n = 66)	1 ( 2)	1 ( 2)	1.0

# Fatigue in Survivors

**Fatigue** one of most prevalent symptoms across diseases after systemic chemotherapy or radiotherapy

➤ **Mental health is the strongest predictor**

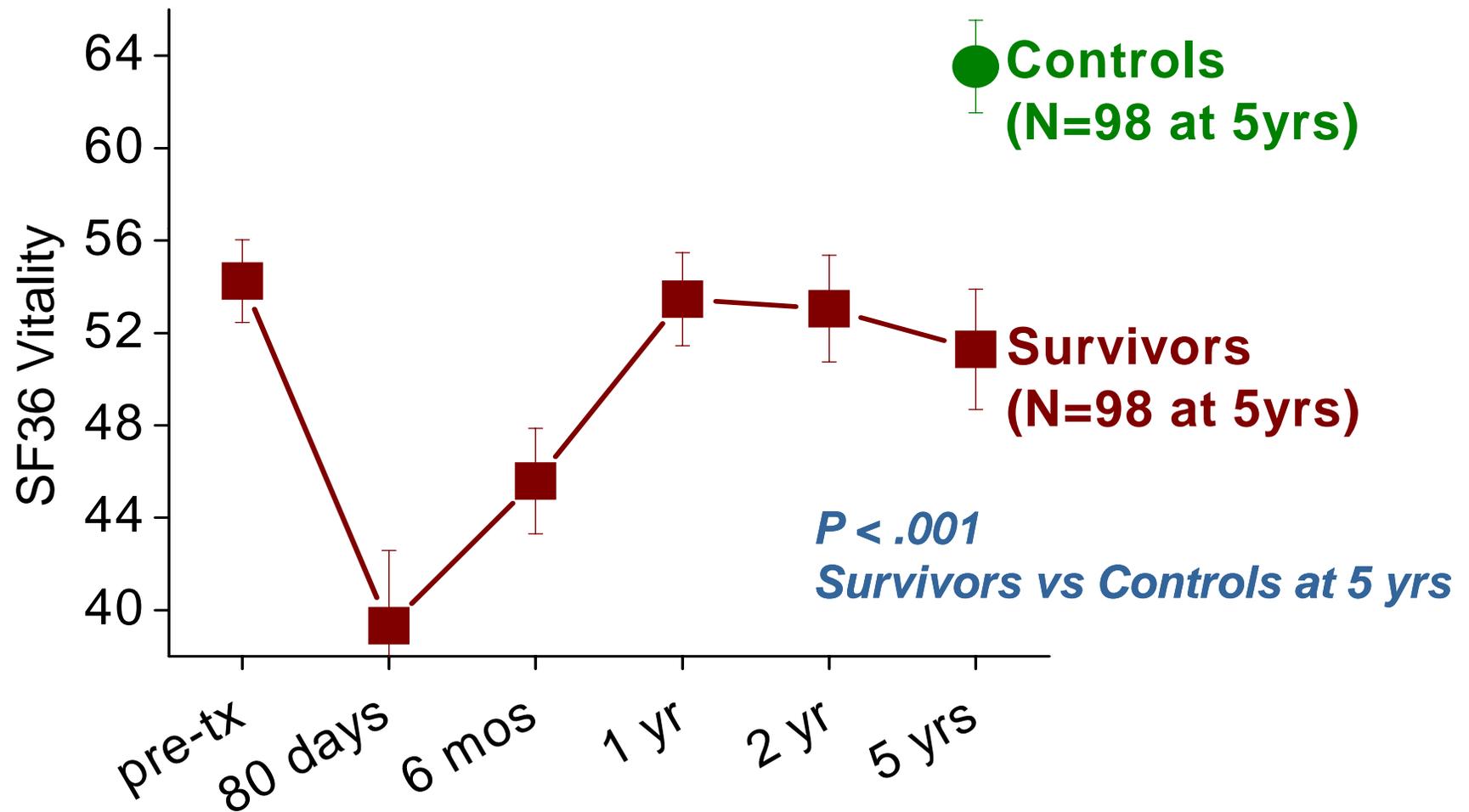
*(Nieboer et al, JCO, 23, 2005)*

- ✓ Mental health may be 'chicken and egg' not risk factor
- ✓ Not anemia or menopausal status – higher hemoglobin less fatigue in other studies
- ✓ Joint and muscle pain reports are related to increased fatigue
- ✓ Relationship of fatigue to stamina and strength / weakness reports needs further investigation

➤ **Biomarkers of fatigue have inconsistent findings**

- ✓ Inflammatory biomarkers predict persistent fatigue after breast cancer *(Bower et al, Collado-Hidalgo et al)*

# 5 Year Cohort (N=199): Vitality (SF36)



Syrjala et al. *J Pain*, 2006: in press

# Physical Limitations in Survivors

- Sedentary lifestyle is often reported in survivors
  - NHL survivors: public health guidelines for exercise were met by 34% before treatment, 6.5% during treatment, 24% after treatment (*Vallance et al, Psycho-Onc, 14, 2005*)

# 5 Year Survivors vs Controls (N=98): Physical Activity Level

	<u>Survivors</u>	<u>Controls</u>
Exercise or sports at least 3x/wk for at least 30 minutes	29%	30%
Avg. # hours active per day	3.9*	5.0
Percent inactive (<2 hr/day moving around)	23%*	7%

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\*  $P < .05$

# Treatments for Physical Limitations

- Most are breast cancer survivor studies of exercise
  - Some include 'rehabilitation' that adds information, education, psychosocial intervention
  - Most provide both cardiorespiratory (aerobics) and some strength and flexibility training
  - **Nearly all benefit fatigue as well as other outcomes (general quality of life, sleep, cognition)**
- Walking, cycling and weight training are most common activities

# Treatments for Physical Limitations

- Treatment completion and maintenance of gains are problems that need to be addressed
- Weight training and exercise do not increase arm circumference or symptoms related to lymphedema (*Ahmed et al, JCO, 24, 2006;*  
*Singh et al, J Strength and Conditioning Research, 20, 2006*)

# Treatments for Physical Limitations

- Complementary treatments are also effective for fatigue
  - Ginseng in breast cancer survivors  
(*Cui et al, Am J Epi, 163, 2006*)
    - ✓ Improved overall quality of life, decreased mortality
  - Tai Chi Chuan improves functional capacity, strength, flexibility  
(*Mustian et al, Supportive Onc 4, 2006*)
  - Yoga results in modest improvement in symptoms  
(*Bower et al. Cancer Control, 12, 2005*)

# 10 Year Moderate-Severe Symptoms

	<b>Survivors</b>	<b>Controls</b>	<b>P</b>
<b><u>1+ musculoskeletal problems</u></b> (not avascular necrosis or hip replacement)	<b>44 (35%)</b>	<b>23 (17%)</b>	<b>.002</b>
<b>Leg cramps</b>	<b>20 (16)</b>	<b>5 ( 4)</b>	<b>&lt; .001</b>
<b>Muscle weakness</b>	<b>22 (16)</b>	<b>9 ( 7)</b>	<b>.045</b>
Joint problems	15 (12)	12 ( 9)	.523
<b>Strictures, stiffness</b>	<b>11 ( 9)</b>	<b>1 ( 1)</b>	<b>.006</b>
<b>Urinary frequency or leaking</b>	<b>41 (30)</b>	<b>21 (16)</b>	<b>.006</b>
<b>Eye problems</b>	<b>30 (22)</b>	<b>10 ( 7)</b>	<b>.001</b>
<b>Memory, attention concerns</b>	<b>27 (20)</b>	<b>9 ( 7)</b>	<b>.003</b>
Sleep problems	19 (14)	12 ( 9)	.42

Syrjala et al, *JCO*, 2005, 23:6596

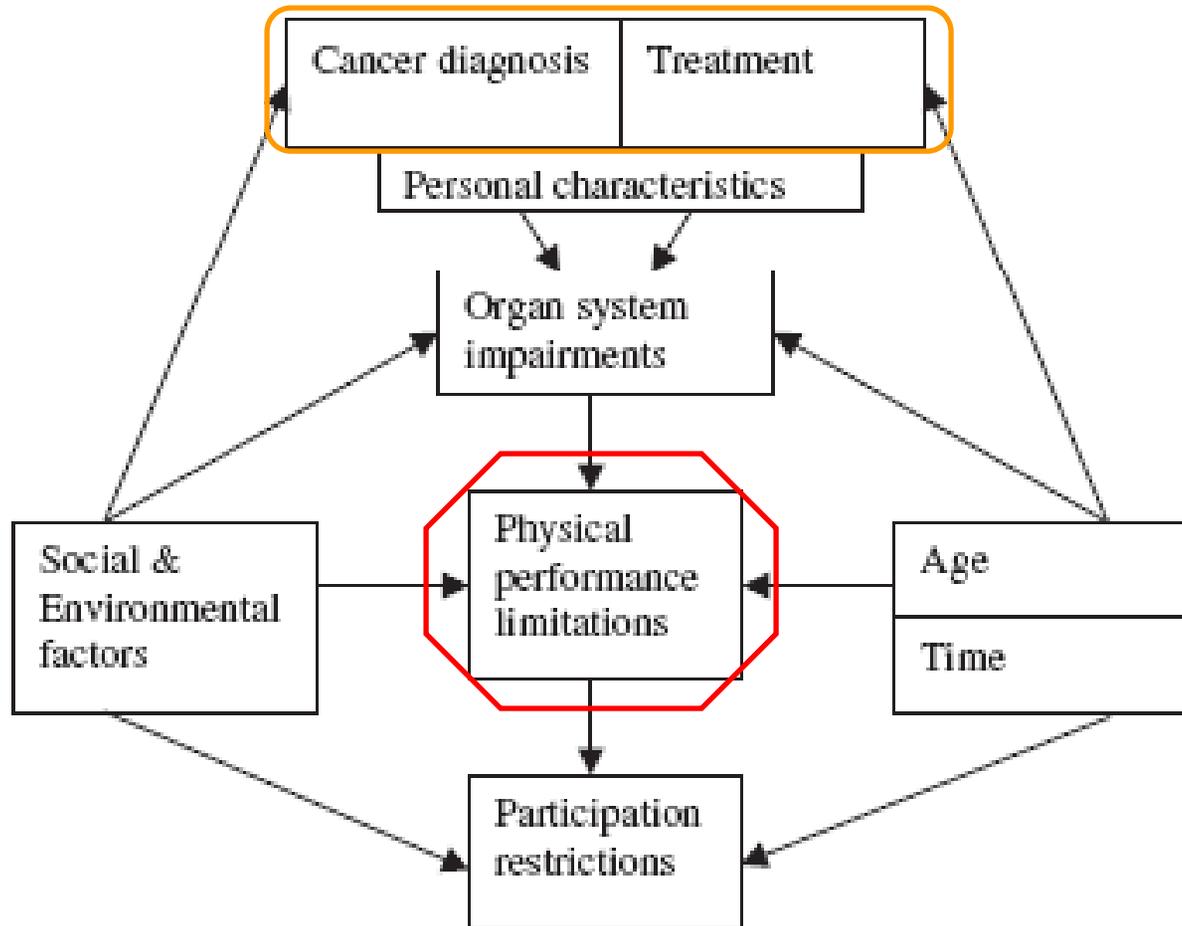
# 5 Year Survivors vs Controls (N=98): Musculoskeletal Problem Prevalence

	<u>Survivors</u>	<u>Controls</u>
<b>% with Moderate to Severe Musculoskeletal Problems</b> (not avascular necrosis)	<b>37%*</b>	<b>15%</b>

\*  $P < .001$  survivors vs controls paired McNemar tests.

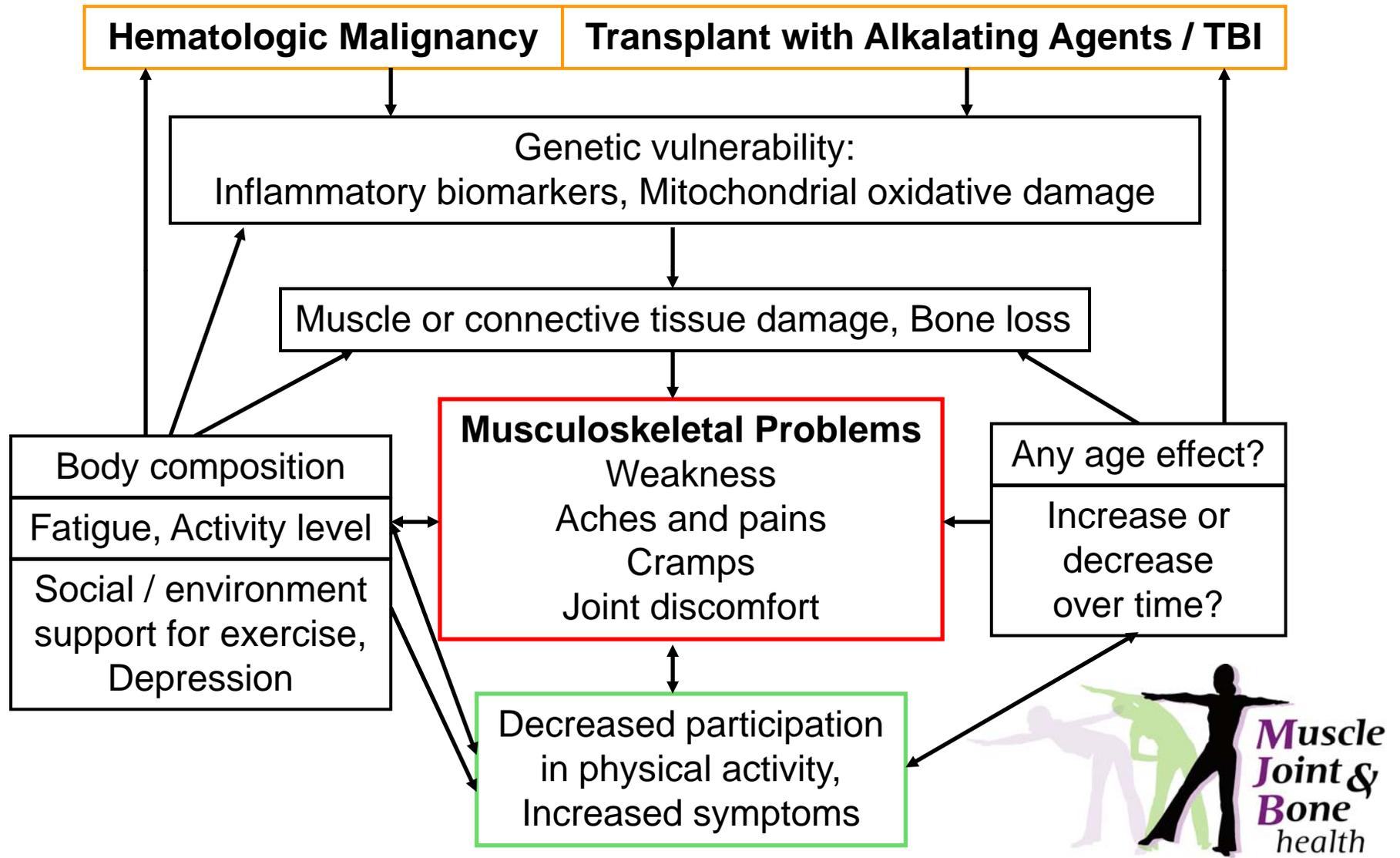
Syrjala et al. *J Pain*, 2006: in press

# Conceptual Model of Physical Limitations, Their Etiologies and Outcome Interactions



Physical performance limitations... Kirsten Ness, Melanie Wall, Michael Oakes, Leslie Robison, James Gurney. *Ann Epidemiol.* 2006; 16, 197-205.

# Conceptual Model Example

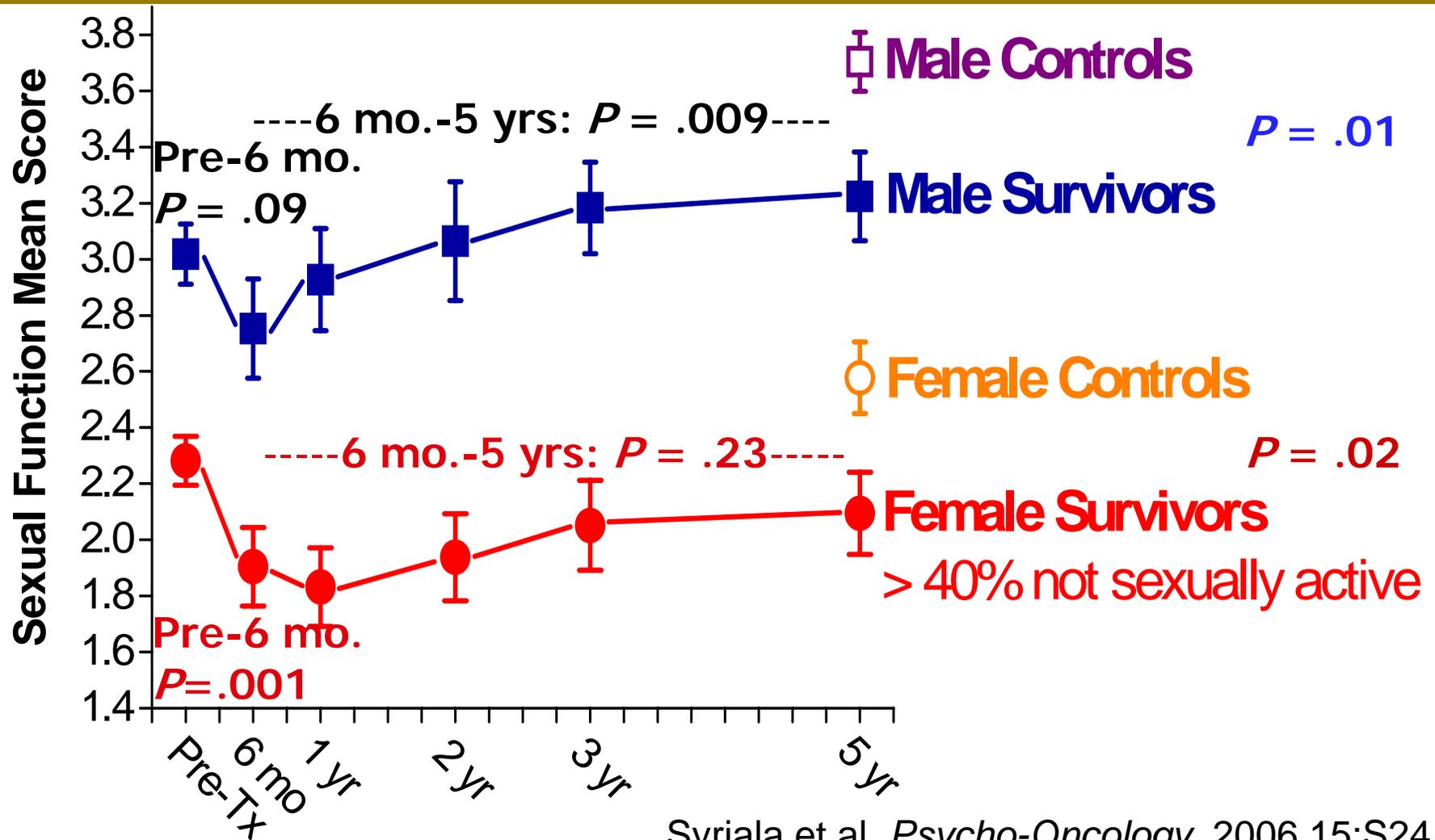


# Physical Limitations in Survivors

## Sexual dysfunction:

- Particularly high in survivors after prostate, breast, and hematologic malignancy (well over 50% for some treatments or diseases)
- Cervical cancer survivors 5+ years who receive radiation therapy have worse function than those who have hysterectomy or controls. (*Frumovitz et al, JCO, 23, 2005*)
- Low testosterone levels impair sex function, not high FSH after testicular cancer. (*Huddart et al, Br J Cancer, 93, 2005*)
  - ✓ Low testosterone increases Body Mass Index (BMI) and blood pressure, not FSH or LH (risk of metabolic syndrome?)
- Few clinical trials. Men concerned but few seek treatment. In clinical trials, attendance and maintenance are main problems. (*Schover et al, Galbraith et al.*)

# Sexual Function Quality & Quantity with controls at 5 years



# RESEARCH ISSUES

**Barrier:** Remote contacting and assessment of long-term survivors. [IRB limits non-mail contact.]

- ◆ Increases potential for enrollment bias.
- ◆ Results commonly depend on patient-reported outcomes.
- ◆ Geographic dispersion increases difficulty of objective testing.

**Barrier:** Prospective records often difficult to get.

- ◆ Increases measurement error in risk factor identification?
- ◆ Risk factors for many problems (sexual function, cognitive function) predate transplant.
- ◆ Difficult to get accurate early treatment history or true baseline.

# RESEARCH ISSUES

**Issue:** Difficult to compare across study results when measures differ. Need reliable, validated measures of symptoms, health problems and health care utilization for survivors.

- ◆ FACT, EORTC not targeted to survivors, SF36 has no symptoms, cancer-related experience).
- ◆ Measures specific to the targeted problem are more sensitive and specific, but then need psychometric testing.
  - ✓ e.g., WOMAC vs our Muscle Joint Bone measure

**Issue:** Who are appropriate controls?

- ◆ Neither general population normative data, nor siblings comparable or accepted for specific survivor cohorts.

# KEY FINDINGS ON PHYSICAL LONG TERM AND LATE EFFECTS

1. A majority of long term survivors physically function well in their lives by their own reports.
2. Long term physical and functional effects that do not resolve with time depend on disease and treatment. Frequent problems include: higher rate of health comorbidities, fatigue/lack of stamina, musculoskeletal problems, decreased participation in activities, sexual dysfunction, urinary frequency or leaking.
3. Exercise treatments are most broadly tested and effective for physical symptoms.
4. It remains unclear whether there are functional late effects similar to 2<sup>nd</sup> cancers, perhaps related to accelerated aging, in 10 - 30 year survivors.

# RESEARCH COLLABORATORS

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