Fatigability and Cancer

What is it? How do we measure it? What are the causes and potential interventions?

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JOHNS HOPKINS
CENTER on AGING & HEALTH

Fatigue

- Fatigue:
  - Subjective lack of physical and/or mental energy perceived to interfere with usual and desired activities
  - Often used interchangeably with tiredness and exhaustion

Alexander NB et al. JAGS. 2010;58:967-975.
Eldadah BA. PM&R. 2010;2:406-413

Fatigue

- Fatigue:
  - Subjective lack of physical and/or mental energy perceived to interfere with usual and desired activities
  - Often used interchangeably with tiredness and exhaustion
- Usually assessed by asking:

In the past month, on average how often have you felt unusually tired during the day? All, most, some, or none of the time? GHSX04

All ○3 Most ○2 Some ○1 None ○0 Don't know ○8 Refused ○7

Fatigue

- Fatigue:
  - Subjective lack of physical and/or mental energy perceived to interfere with usual and desired activities
  - Often used interchangeably with tiredness and exhaustion
- Usually assessed by asking:

During the past month, what category best describes your usual energy level, using a scale from 0 to 10, where 0 is no energy at all and 10 is the most energy you have ever had? GHSX06

No energy at all										Most energy	DK	Refused
○	○	○	○	○	○	○	○	○	○	○	○	○
0	1	2	3	4	5	6	7	8	9	10	88	77

Why is Fatigue Difficult to Measure?

Fatigue: 8/10

Fatigue: 8/10

Fatigue: 7/10

Fatigue: 9/10

Higher Activity ← Lower Activity

Lower Fatigability → Higher Fatigability

Fatigue vs. Fatigability

- Fatigability:
  - Whole-body measure describing fatigue in relation to a standardized task in terms of time, distance, and/or speed
    - Perceived fatigability
    - Performance fatigability

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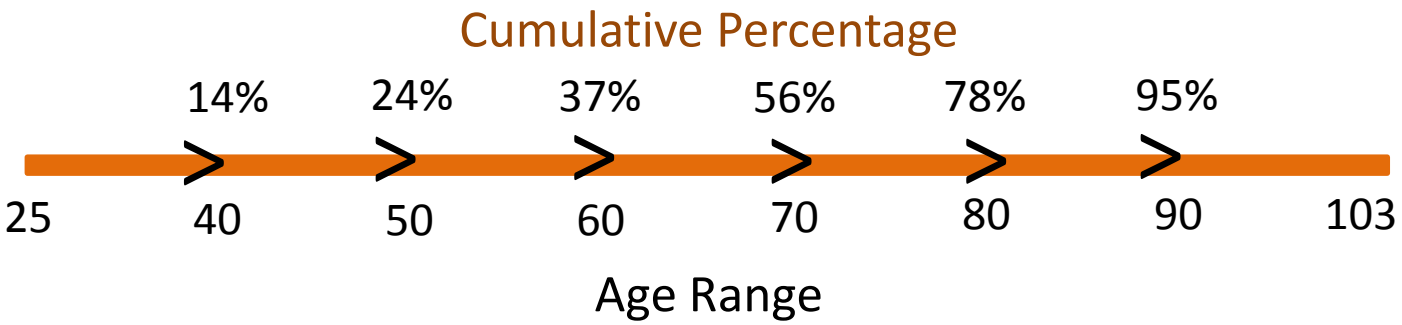
BLSA BALTIMORE LONGITUDINAL STUDY OF AGING

Study Population

- Baltimore Longitudinal Study of Aging ("BLSA")
  - Clinical Research Program of the NIA - IRP
  - Conducted in Baltimore since 1958
  - Study of "normative" aging
  - Healthy upon enrollment: free of cognitive deficits & disability
- Current enrollment: 1330 (52.9% female)
  - Age 80 & older: assessed annually
  - Age 60-79: assessed every two years
  - Under age 60: assessed every 4 years



Measures of Fatigability in the Baltimore Longitudinal Study of Aging

- **Perceived Fatigability:**
  - Use the Borg Rating of Perceived Exertion (RPE) scale to understand fatigability in relation to a standardized treadmill walk

- **Performance Fatigability:**
  - Assess performance during a 400m walk done “as quickly as possible”

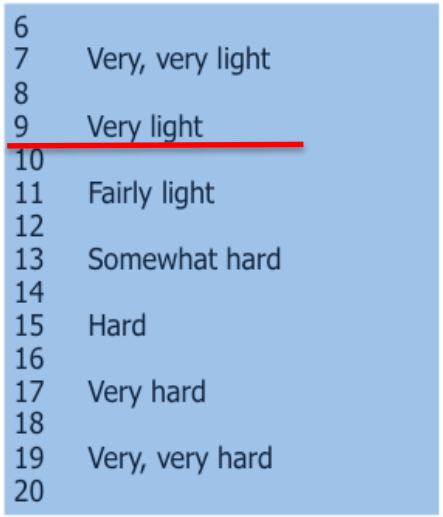
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

NIH National Institute on Aging

Simonsick et al. JAGS 2014

Measures of Fatigability in the Baltimore Longitudinal Study of Aging

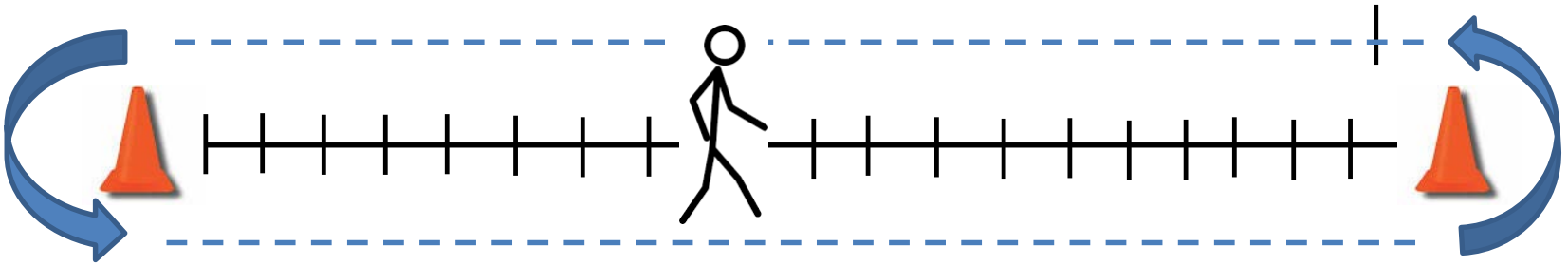
- **Perceived Fatigability:**
  - 5 min treadmill walk at 1.5 mph (.67 m/s), 0% grade
  - Immediately following, participants give their Rating of Perceived Exertion (RPE) from the Borg scale
  - **Those with a RPE of ≥10 (e.g., High Fatigability) have been shown to have greater risk of decline in physical function at follow up**



Simonsick et al. JAGS 2014

Performance fatigability

- **Long Distance Corridor Walk** consisting of a **400m** walk "done as quickly as possible" without running
- Total time and **10** lap by lap (**40m**) split times are recorded
  - >5:00 min considered reduced performance
  - 6:30– 7:00 min times associated with poor mobility



Assessing Fatigability in Mobility-Intact Older Adults

Eleanor M. Simonsick, PhD, Jennifer A. Schrack, PhD,† Nancy W. Glynn, PhD,‡ and Luigi Ferrucci, MD, PhD**

JAGS 2014

Fatigued, but Not Frail: Perceived Fatigability as a Marker of Impending Decline in Mobility-Intact Older Adults

Eleanor M. Simonsick, PhD, Nancy W. Glynn, PhD,† Gerald J. Jerome, PhD,‡ Michelle Shardell, PhD,* Jennifer A. Schrack, PhD,§ and Luigi Ferrucci, MD, PhD**

JAGS 2016

Perceived Fatigability and Objective Physical Activity in Mid- to Late-Life

Amal A. Wanigatunga, PhD, MPH,[1,2] Eleanor M. Simonsick, PhD,[3] Vadim Zipunnikov, PhD,[4] Adam P. Spira, PhD,[2,5,6] Stephanie Studenski, MD, MPH,[3] Luigi Ferrucci, MD, PhD,[3] and Jennifer A. Schrack, PhD[1,2]

J Gerontol A Biol Sci Med Sci, 2017

Fatigability and functional performance among older adults with low-normal ankle-brachial index: Cross-sectional findings from the Baltimore Longitudinal Study of Aging

Atherosclerosis 272 (2018) 200–206

Pablo Martinez-Amezcua [a, b, *], Kunihiro Matsushita [a], Eleanor M. Simonsick [c], Luigi Ferrucci [c], Jennifer A. Schrack [a, b]

Longitudinal Relationship Between Interleukin-6 and Perceived Fatigability Among Well-Functioning Adults in Mid-to-Late Life

Amal A. Wanigatunga, PhD, MPH,[1,2] Ravi Varadhan, PhD, PhD,[2,3] Eleanor M. Simonsick, PhD,[4] Olga D. Carlson, PhD,[4] Stephanie Studenski, MD, MPH,[4] Luigi Ferrucci, MD, PhD,[4] and Jennifer A. Schrack, PhD[1,2,4]

Journals of Gerontology: Medical Sciences

Characterizing Cancer in the BLSA

- Excluded squamous and basal cell skin cancers
- Grouped by general cancer type
- Majority of patients are Prostate and Breast

Cancer Type	N
Breast	53
Prostate	127
GI (Colon/stomach/pancreatic/liver)	24
OB/GYN (Cervical/endometrial/ovarian)	20
Melanoma	42
Lung	11
Lymphoma/Leukemia	19
Other (Bladder/Brain/Thyroid/"Other cancer")	75
Total (excluding non-melanoma skin cancers)	371

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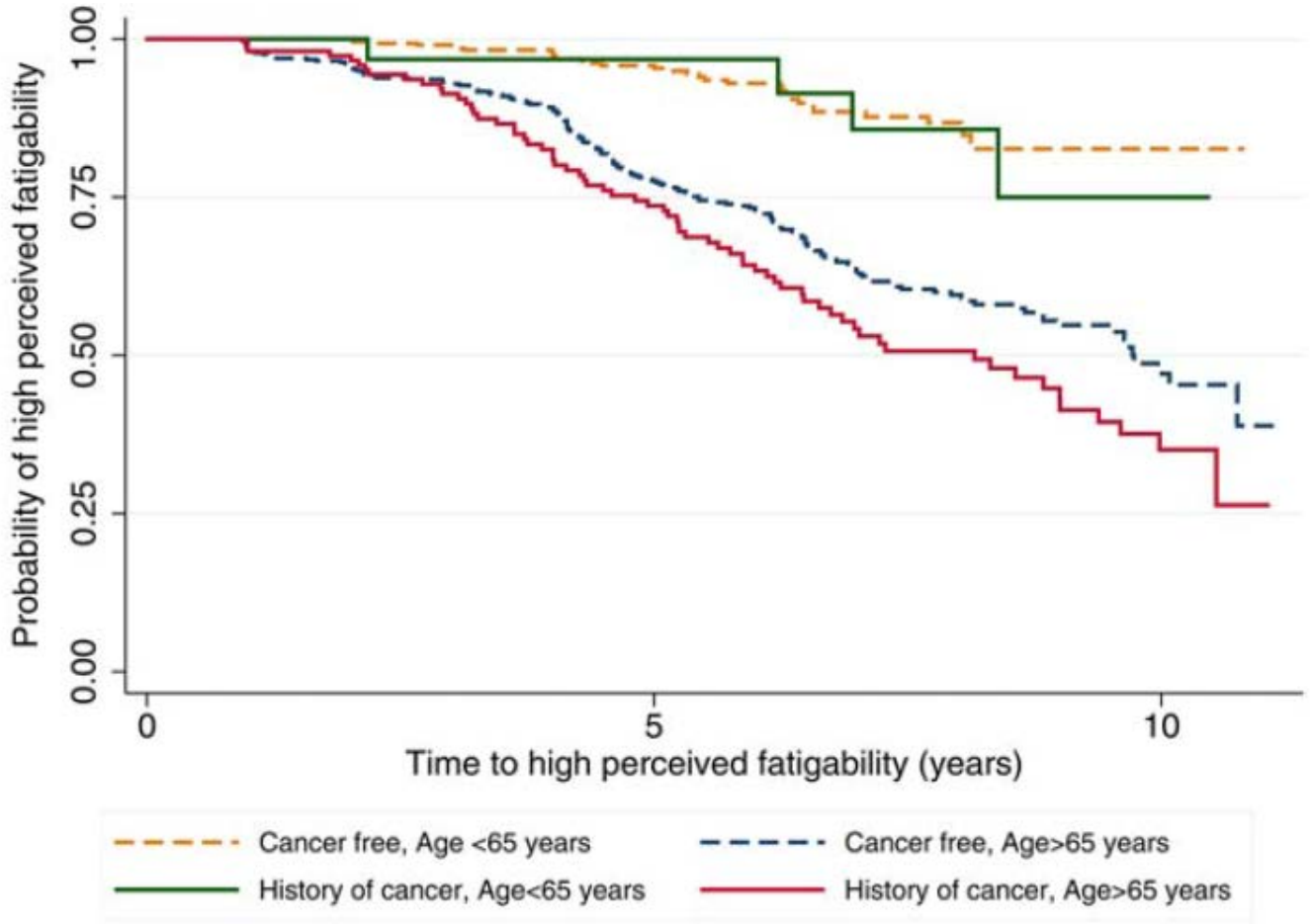
Participant Characteristics

N = 1665	Prevalent Cancer (N = 248)	Incident Cancer (N = 86)	No Cancer (N = 1331)
Age	73.6 ± 9.9	74.1 ± 12.1	69.6 ± 15.6
Male	61.3%	65.1%	44.9%
White Race	83.1%	68.6%	69.3%
Ever Smoked	51.4%	53.6%	41.1%
Comorbidities (No.)	1.4 ± 1.2	1.4 ± 1.3	1.2 ± 1.3

Median age at cancer diagnosis: 66 years (IQR: 57-75 years)

Average follow-up time: 4.1 years

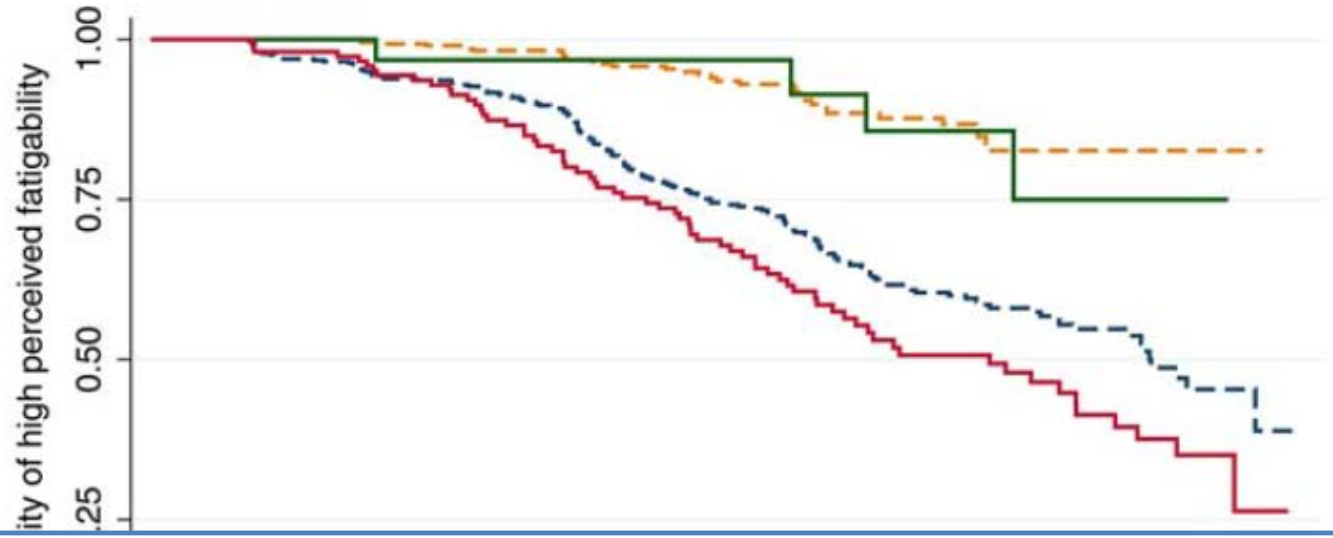
Perceived Fatigability by Age & Cancer History



Fatigability and Endurance Performance in Cancer Survivors: Analyses From the Baltimore Longitudinal Study of Aging

Gresham, Cancer 2018

Perceived Fatigability by Age & Cancer History



What does this mean?

- < 65 years + cancer = 34% greater risk of high fatigability
- ≥ 65 years + cancer = 3 times greater risk of high fatigability

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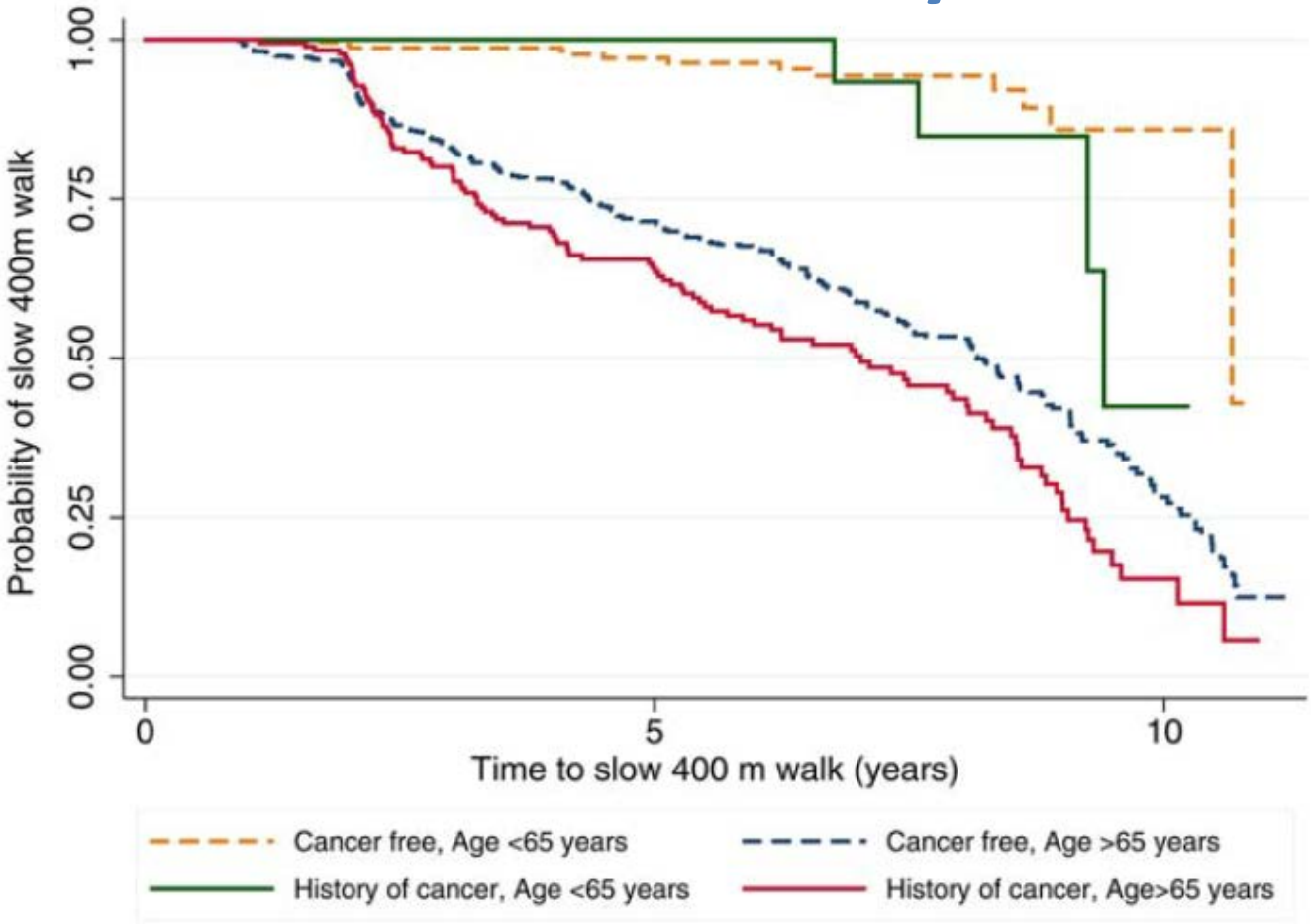
Gresham, Cancer 2018

Endurance Performance by Age & Cancer History



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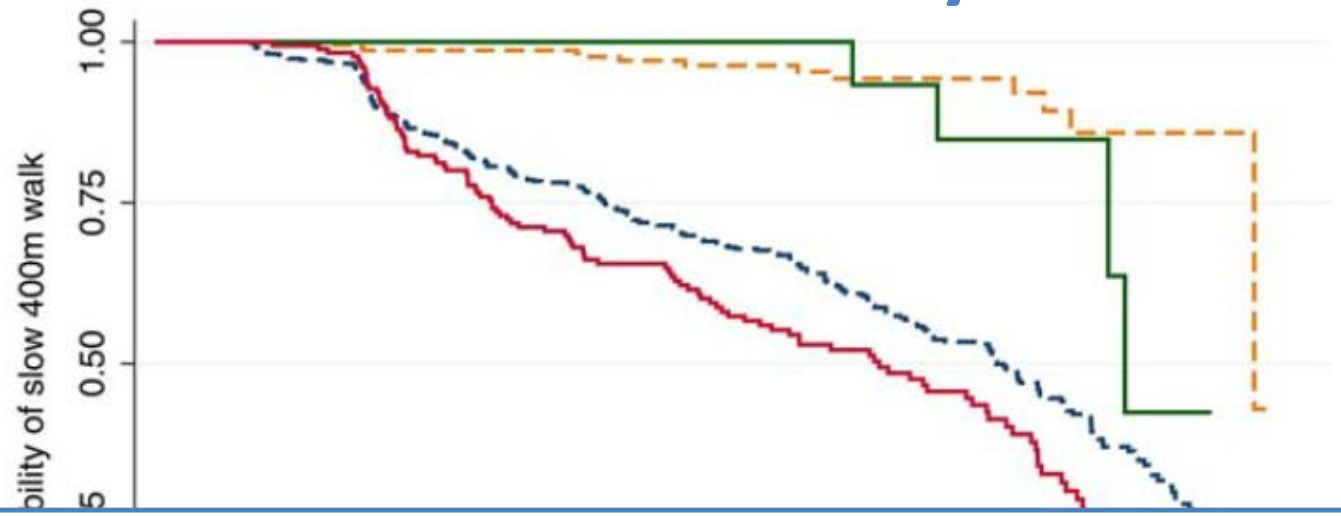


What does this mean?

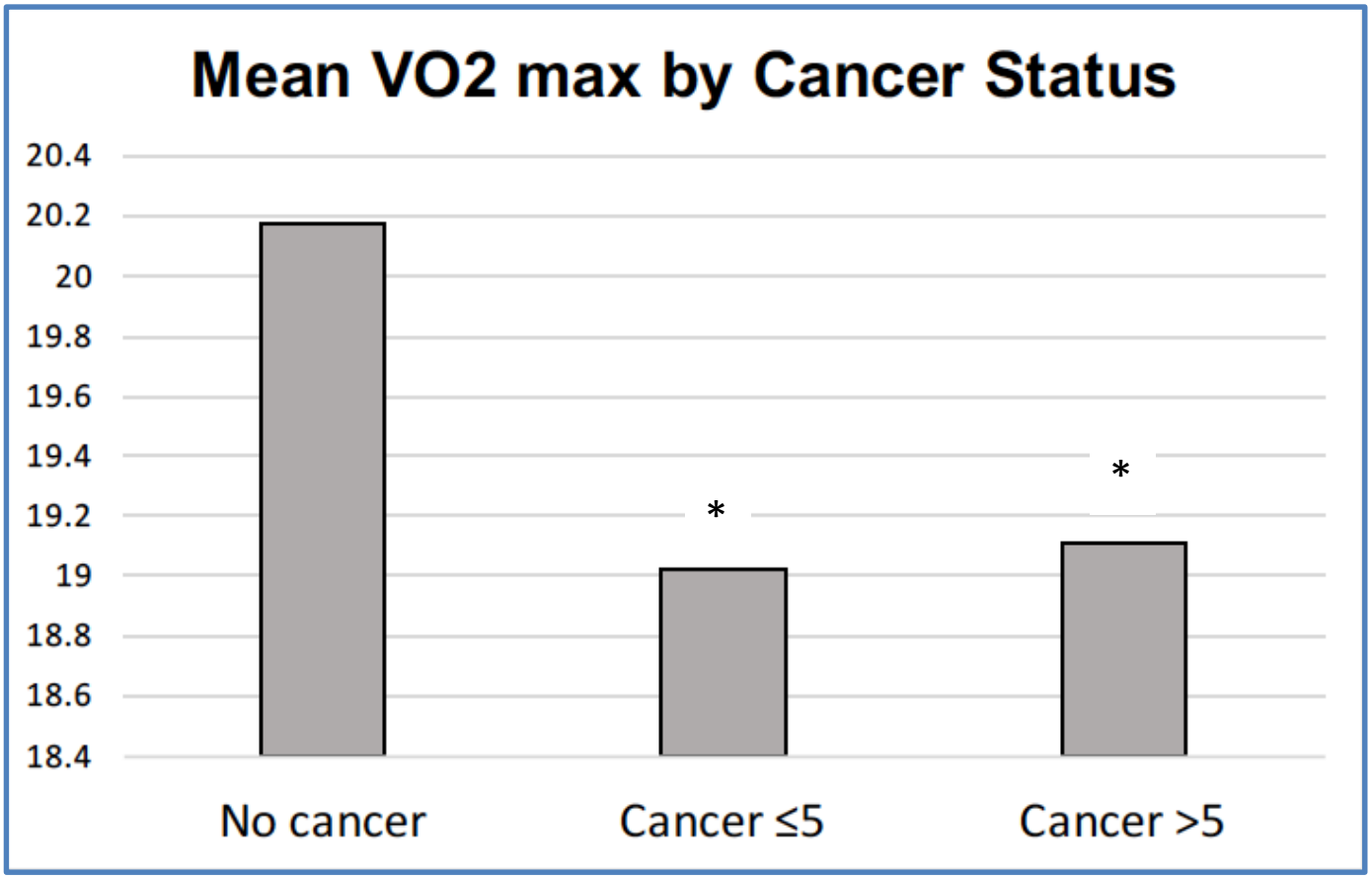
- < 65 years + cancer = 42% greater risk of low endurance
- ≥ 65 years + cancer = 8.3 times greater risk of low endurance

Fatigability and Endurance Performance in Cancer Survivors: Analyses From the Baltimore Longitudinal Study of Aging

Gresham, Cancer 2018

Potential Contributors:

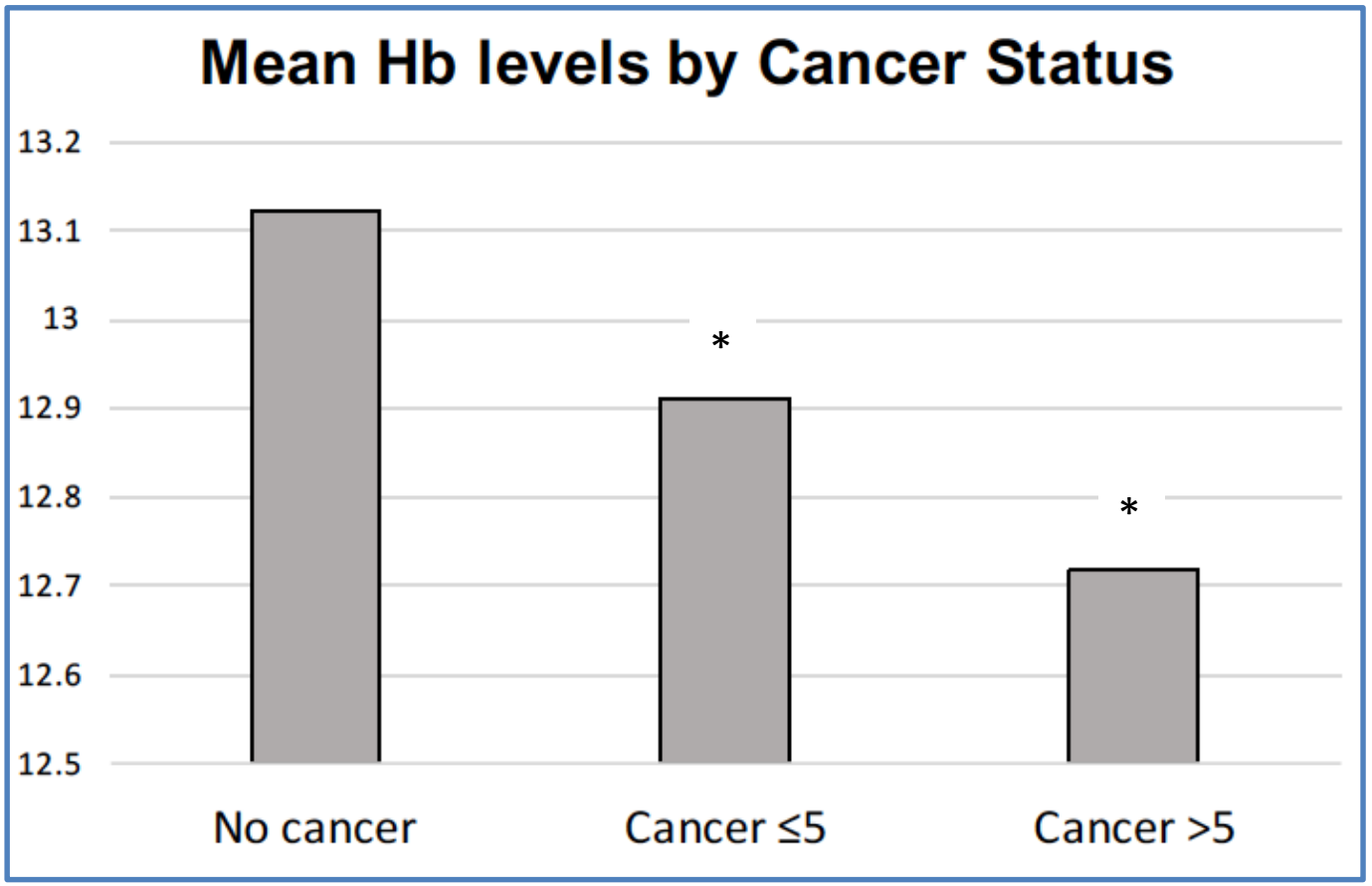
Lower Cardiorespiratory Fitness



Unpublished data

Potential Contributors:

Lower Hemoglobin (higher anemia)



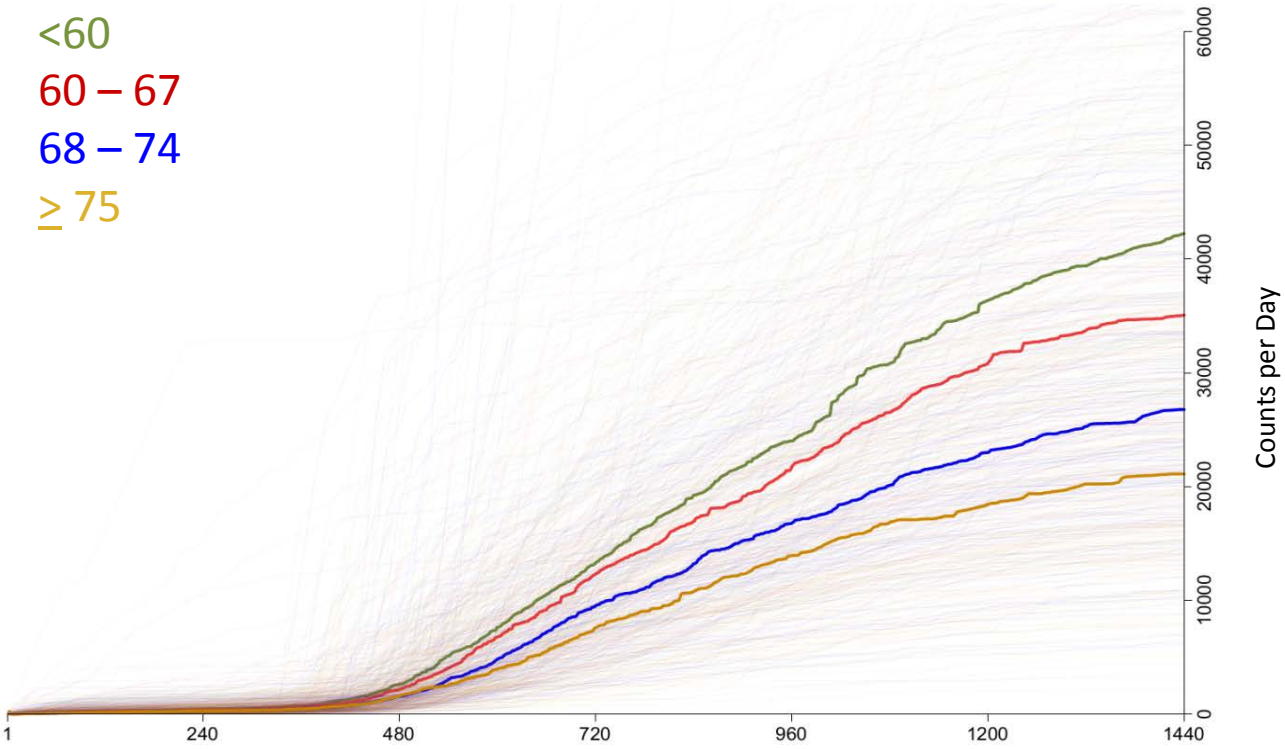
Unpublished data

What about the physical activity?

- What can we learn by monitoring daily physical activity to derive:
  - Total daily activity volume
  - Diurnal (circadian) rhythms of activity
  - Characteristics of activity
    - Length of activity bouts
    - Degree of activity fragmentation

Assessing the "Physical Cliff": Detailed Quantification of Age-Related Differences in Daily Patterns of Physical Activity

Jennifer A. Schrack,[1,2] Vadim Zipunnikov,[3] Jeff Goldsmith,[4] Jiawei Bai,[3] Eleanor M. Simonsick,[2] Ciprian Crainiceanu,[3] and Luigi Ferrucci[2]



1.3% loss of activity per year from mid-to-late life

N = 611, BLSA subjects

Schrack et al, JGMS 2014

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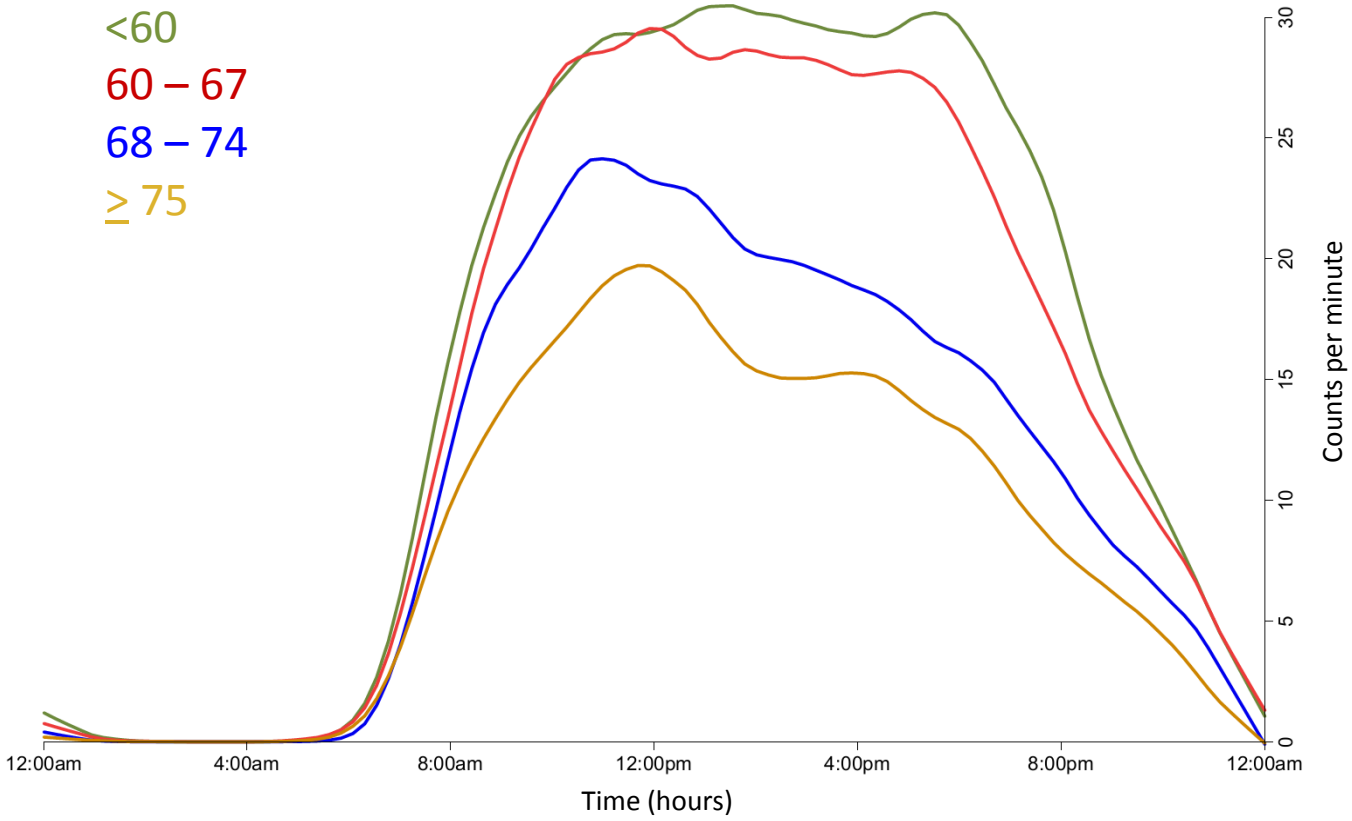
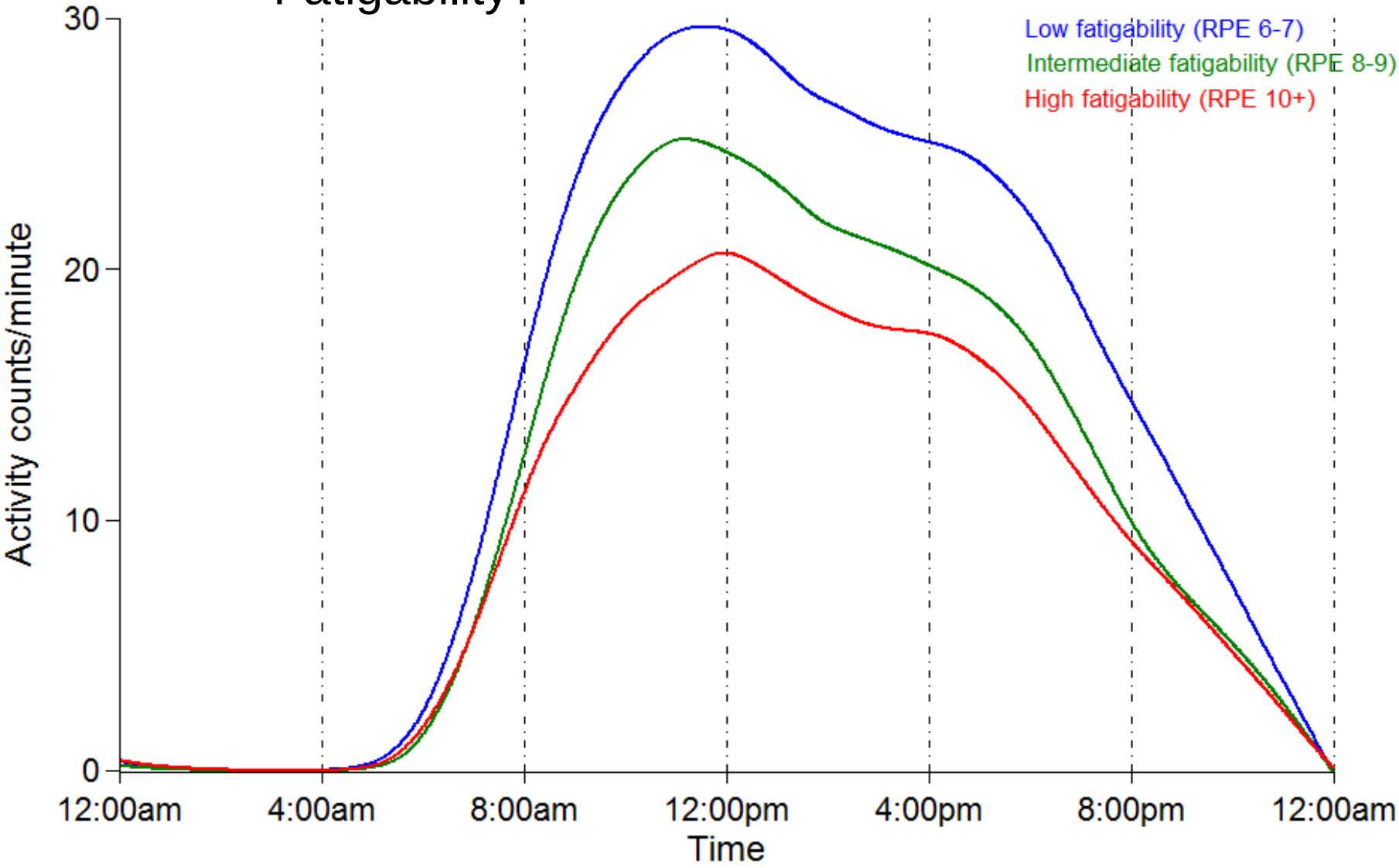


N = 611, BLSA subjects

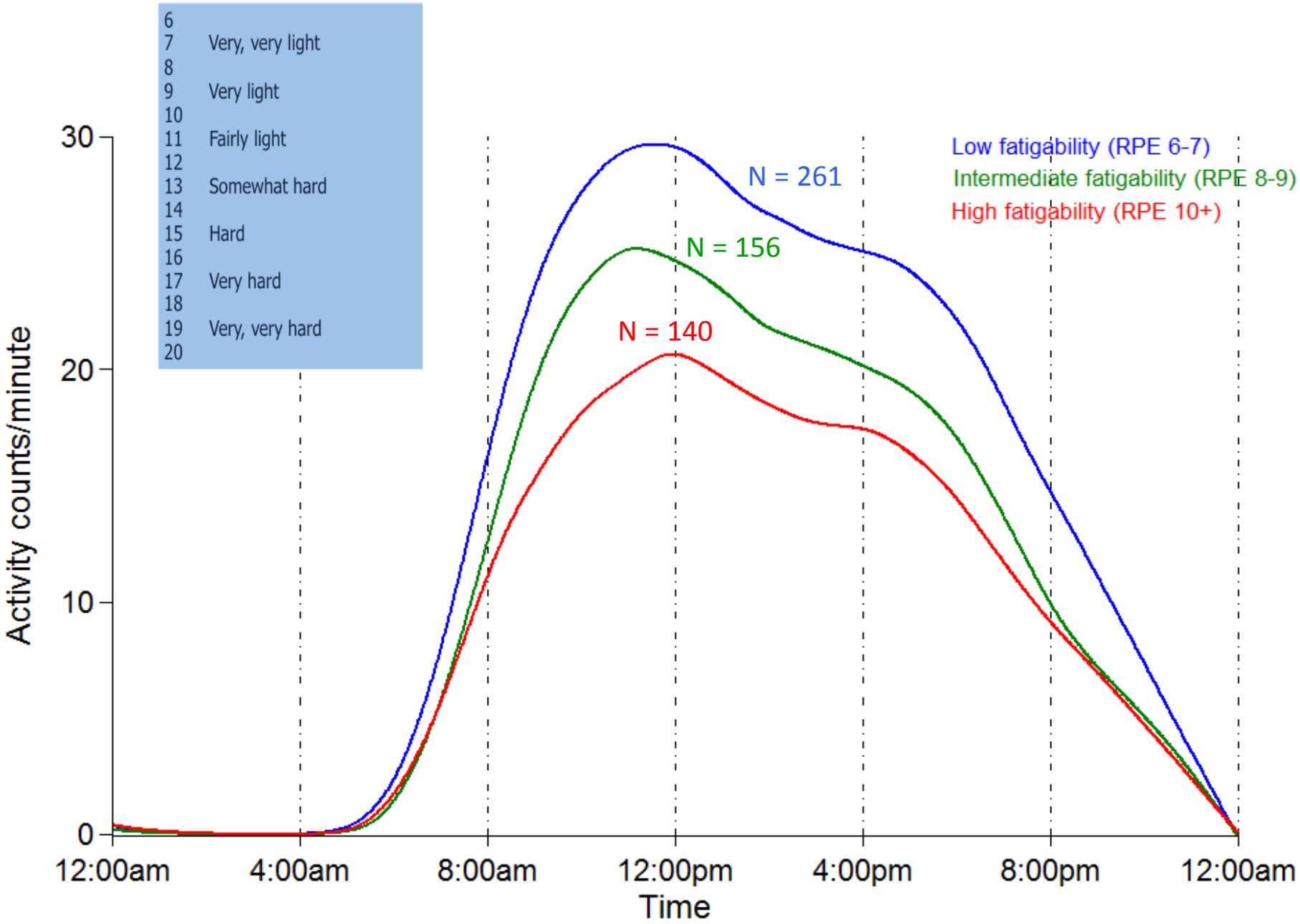
Schrack et al, JGMS 2014

What Can Diurnal Patterns Tell Us About Fatigability?



Note: RPE – rate of perceived exertion

Wanigatunga, et al, JGMS 2017



Note: RPE – rate of perceived exertion
Wanigatunga, et al, JGMS 2017

Physical activity accumulation patterns with aging

Activity fragmentation

Physical function

Physical activity

10 minutes

8 minutes

2 minutes

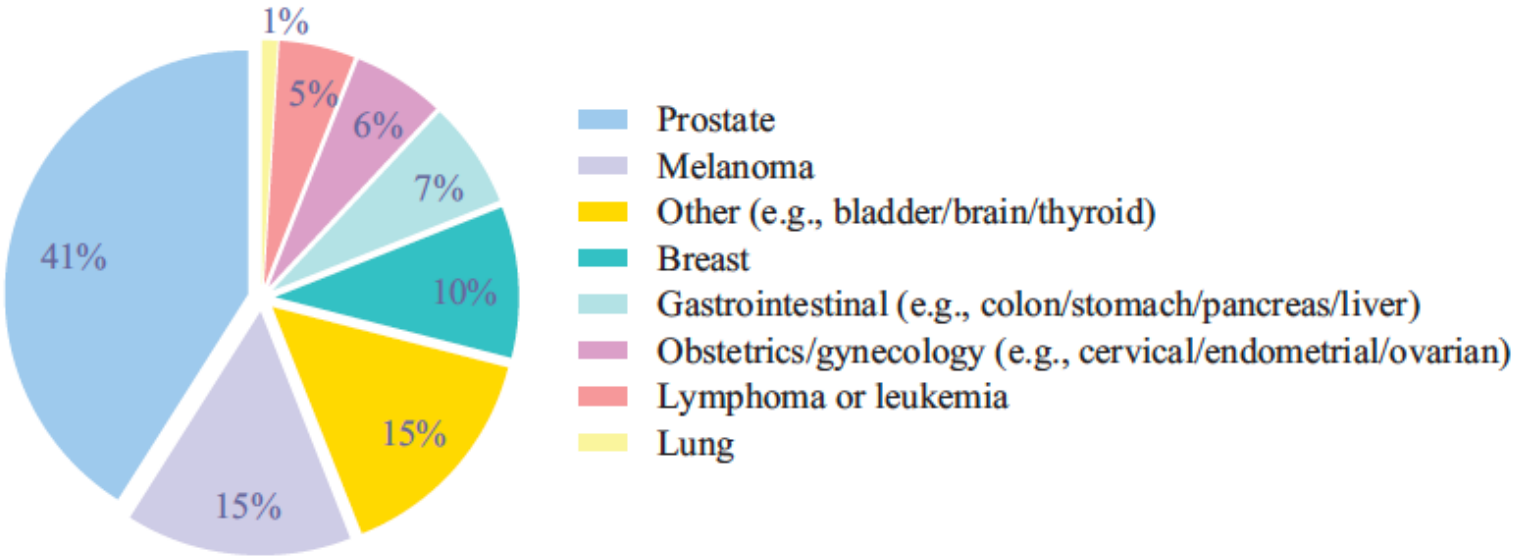
5 minutes

3 minutes

2 minutes

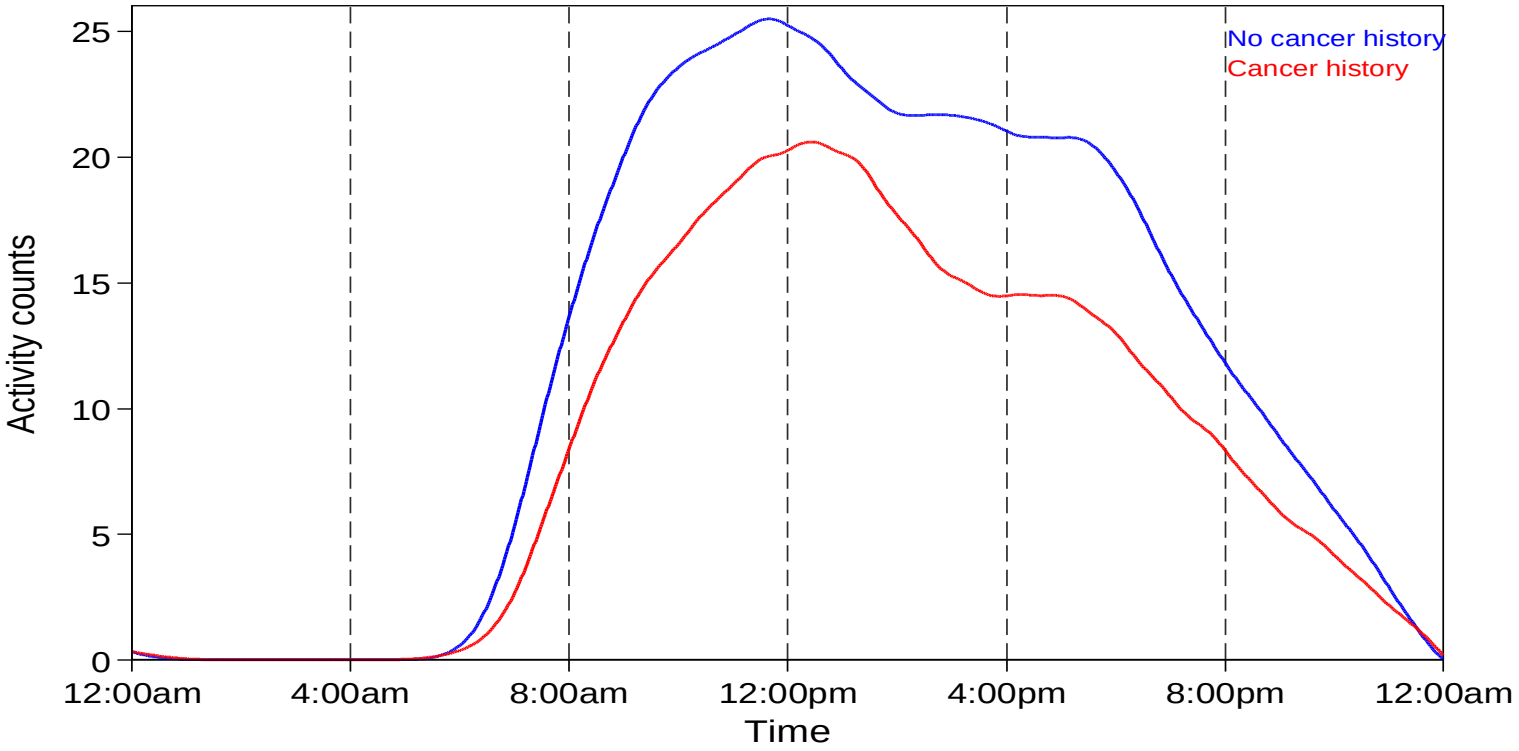
Contrasting Characteristics of Daily Physical Activity in Older Adults by Cancer History

Amal A. Wanigatunga, PhD, MPH[1,2]; Gillian K. Gresham, PhD[1,3]; Pei-Lun Kuo, MD, MPH[1,2,4,5]; Pablo Martinez-Amezcua, MD, MHS[1,2]; Vadim Zipunnikov, PhD[4]; Sydney M. Dy, MD, MS[6]; Eleanor M. Simonsick, PhD[5]; Luigi Ferrucci, MD, PhD[5]; and Jennifer A. Schrack, PhD[1,2,5]



Physical Activity Quantities and Patterns

Smoothed 24-hour median activity counts per minute by cancer status



-Cancer survivors averaged lower amounts of total daily physical activity than those with no history of cancer

-Difference in activity was equivalent to about 5 years of age

Contrasting Characteristics of Daily Physical Activity in Older Adults by Cancer History

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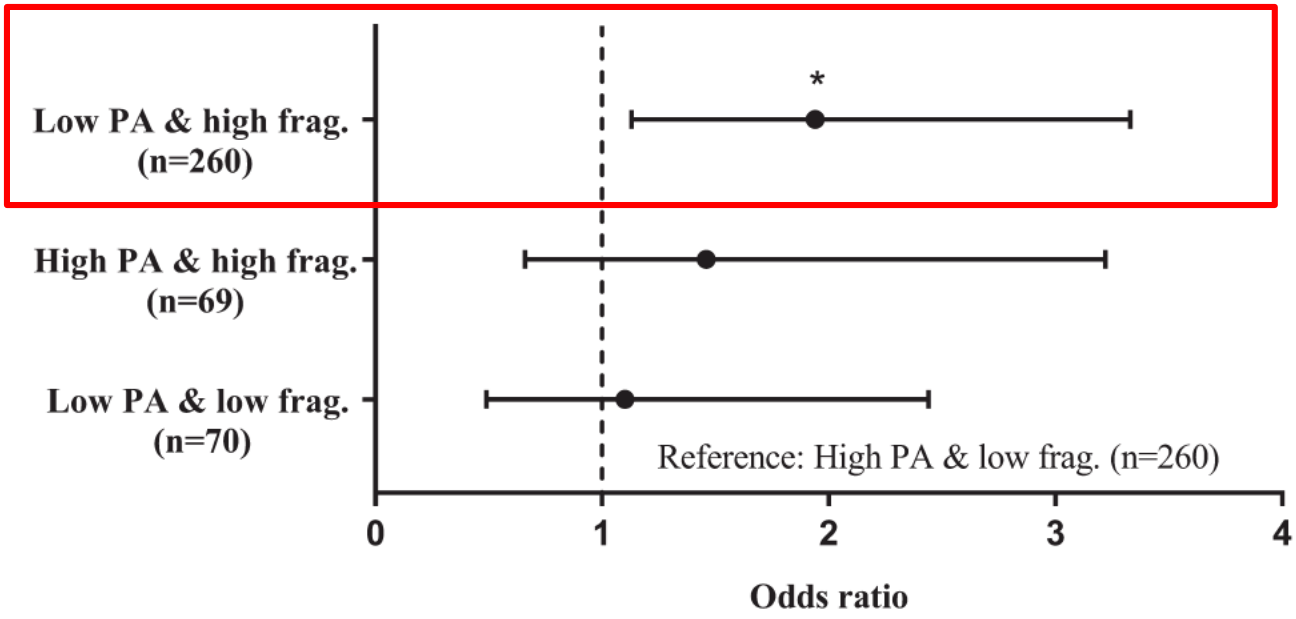

Cancer survivors were nearly twice as likely to have both low physical activity and highly fragmented activity

Wanigatunga, Cancer 2018

Summary

- Older adults with a history of cancer have:
  - Higher perceived fatigability after a standardized walking task
    - 3 times greater risk
  - Lower walking endurance (400 meters)
    - 8.3 times greater risk
    - Averaged 42 seconds slower
- This is reflected in quantities and patterns of daily physical activity
  - Lower levels of daily physical activity
    - Equivalent to about 5 years of age
  - More fragmented daily profiles of physical activity

Still to be answered…

- How do these results compare to clinical populations?
  - BLSA is a study of “healthy” aging (survivors)
  - Need to compare to cancer patients and/or recent survivors
- How does fatigability differ by type of cancer?
  - Differences by stage of cancer?
- What are the effects of treatment?
  - Are certain types of treatment more damaging long term? Differences in body composition?
- What is the role of sleep?

How do we treat fatigability?

- Treatments for fatigability are not well defined
- Differences in fatigability by treatment could inform clinical decision making for immediate survival and long term quality of life
- Physical activity interventions are promising to increase endurance and maintain quality of body composition
  - May be problematic in sicker populations
  - Long term adherence of traditional interventions is questionable
  - Effectiveness of self-paced interventions using wearables is being investigated in various populations

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Amal Wanigatunga, PhD, MPH

Vadim Zipunnikov, PhD

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In Memoriam:
Arti Hurria, MD

Director, Center for Cancer and Aging, City of Hope, CA

Cancer in the Older Adult: Implications for Therapy and Future Research

Mina S. Sedrak, MD, MS Arti Hurria, MD