Exercise Oncology: implications for Recurrence and Survival

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PROSTATE CANCER SURVIVORSHIP

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Physical Activity and Risk of Cancer

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Original Investigation

Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults

Steven C. Moore, PhD, MPH; I-Min Lee, MBBS, ScD; Elisabete Weiderpass, PhD; Peter T. Campbell, PhD; Joshua N. Sampson, PhD; Cari M. Kitahara, PhD; Sarah K. Keadle, PhD, MPH; Hannah Arem, PhD; Amy Berrington de Gonzalez, DPhil; Patricia Hartge, ScD; Hans-Olov Adami, MD, PhD; Cindy K. Blair, PhD; Kristin B. Borch, PhD; Eric Boyd, BS; David P. Check, BS; Agnès Fournier, PhD; Neal D. Freedman, PhD; Marc Gunter, PhD; Mattias Johannson, PhD; Kay-Tee Khaw, MD, MSc, PhD; Martha S. Linet, MD; Nicola Orsini, PhD; Yikyung Park, ScD; Elio Riboli, MD; Kim Robien, PhD; Catherine Schairer, PhD; Howard Sesso, ScD, MPH; Michael Spriggs, BS; Roy Van Dusen, MS; Alicja Wolk, DMSc; Charles E. Matthews, PhD; Alpa V. Patel, PhD

JAMA Internal Medicine

Pooled data from 12 prospective US and European cohorts with self-reported PA
Looked at 26 types of cancer in 1.44 million adults, followed for median of 11 years
186,932 cancers

Esophageal adenocarcinoma	HR, 0.58 (95% CI, 0.37-0.89)
Liver	HR, 0.73 (95% CI, 0.55-0.98)
Lung	HR, 0.74 (95% CI, 0.71-0.77)
Kidney	HR, 0.77 (95% CI, 0.70-0.85)
Gastric cardia	HR, 0.78 (95% CI, 0.64-0.95)
Endometrial	HR, 0.79 (95% CI, 0.68-0.92)
Myeloid leukemia	HR, 0.80 (95% CI, 0.70-0.92)
Myeloma	HR, 0.83 (95% CI, 0.72-0.95)
Colon	HR, 0.84 (95% CI, 0.77-0.91)
Head and neck	HR, 0.85 (95% CI, 0.78-0.93)
Rectal	HR, 0.87 (95% CI, 0.80-0.95)
Bladder	HR, 0.87 (95% CI, 0.82-0.92)
Breast	HR, 0.90 (95% CI, 0.87-0.93)

"PA has far reaching value for cancer prevention"

Moore et al. JAMA Intern Med 176(6):816-825, 2016

Physical Activity and Survival After Breast Cancer Diagnosis

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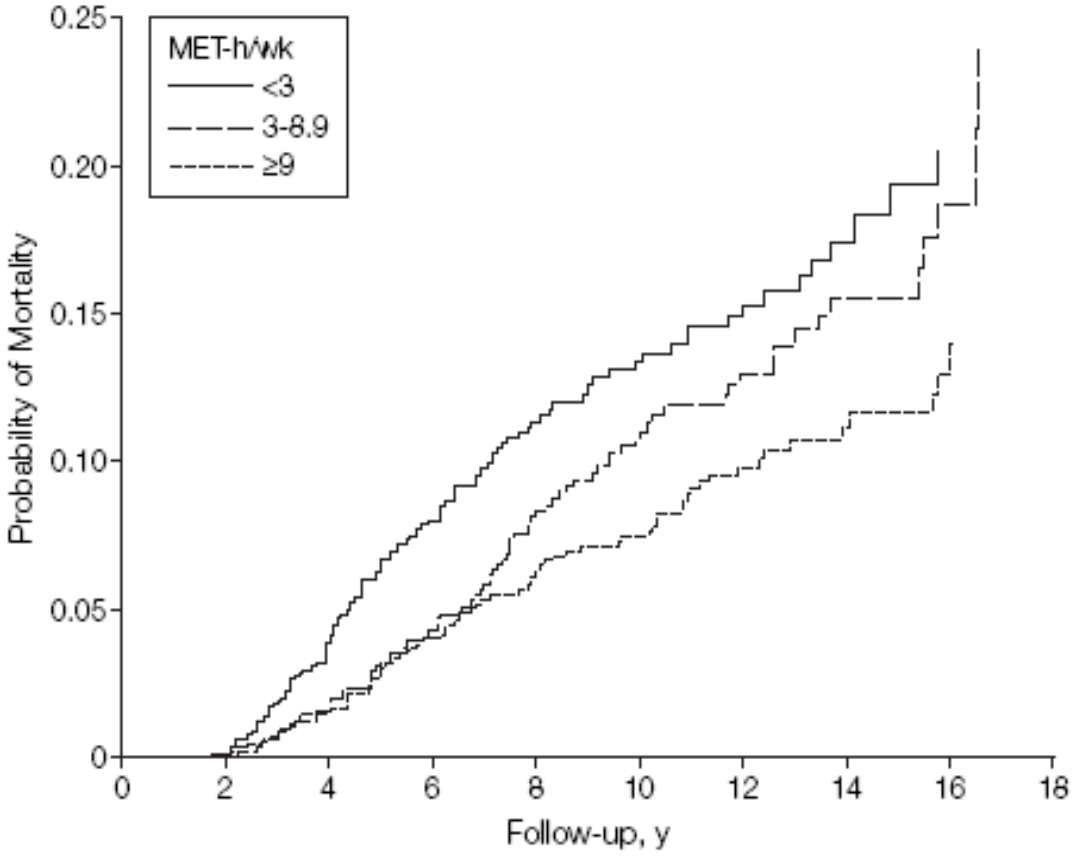
Prospective observational study n=2987 female registered nurses in the Nurses' Health Study

Protective association between increased PA after diagnosis and recurrence, cancer-related mortality, and overall mortality (stage I-III breast cancer)



No. at Risk

Physical Activity, MET-h/wk									
<3	959	957	809	573	407	286	222	83	43
3-8.9	862	862	767	569	489	372	184	84	31
≥9	1166	1166	1066	773	692	449	290	164	86

BCa deaths
Adj. RR 0.80 (0.60 – 1.06) 3-8.9 M-h/wk
Adj. RR 0.50 (0.31 – 0.82) 9-14.9 M-h/wk

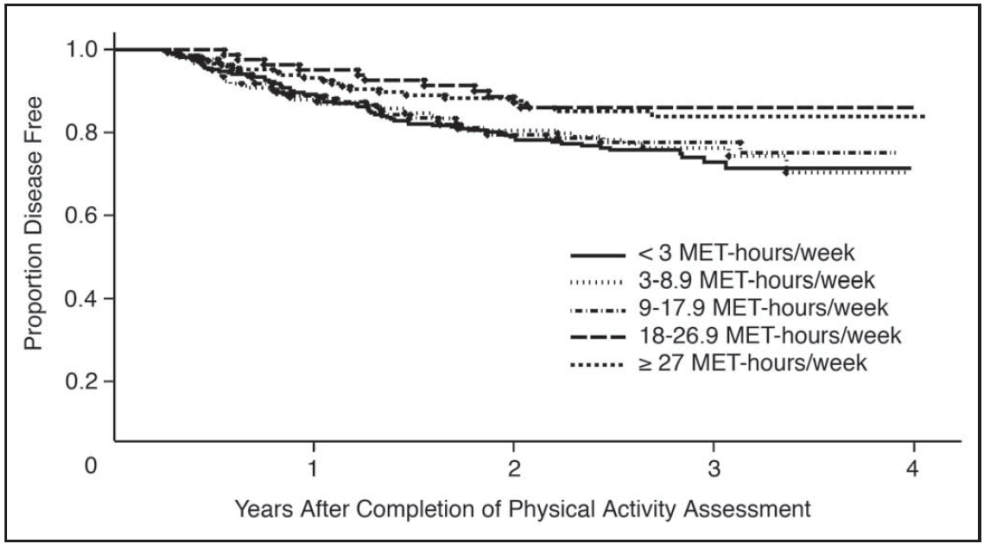
Holmes et al. *JAMA* 293:2479-2486, 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Impact of Physical Activity on Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803

Jeffrey A. Meyerhardt, Denise Heseltine, Donna Niedzwiecki, Donna Hollis, Leonard B. Saltz, Robert J. Mayer, James Thomas, Heidi Nelson, Renaud Whittom, Alexander Hantel, Richard L. Schilsky, and Charles S. Fuchs

Prospective observational study
N= 832 patients
PA 6 months after completing adjuvant chemotherapy
Median follow-up 2.7 years



Adj. HR 0.51 (0.26 – 0.97) 18-26.9 M-h/wk
Adj. HR 0.55 (0.33 – 0.91) ≥ 27 M-h/wk

Improvement in DFS

~ 6 or more hours walking/week

J Clin Oncol 24:3535-3541, 2006

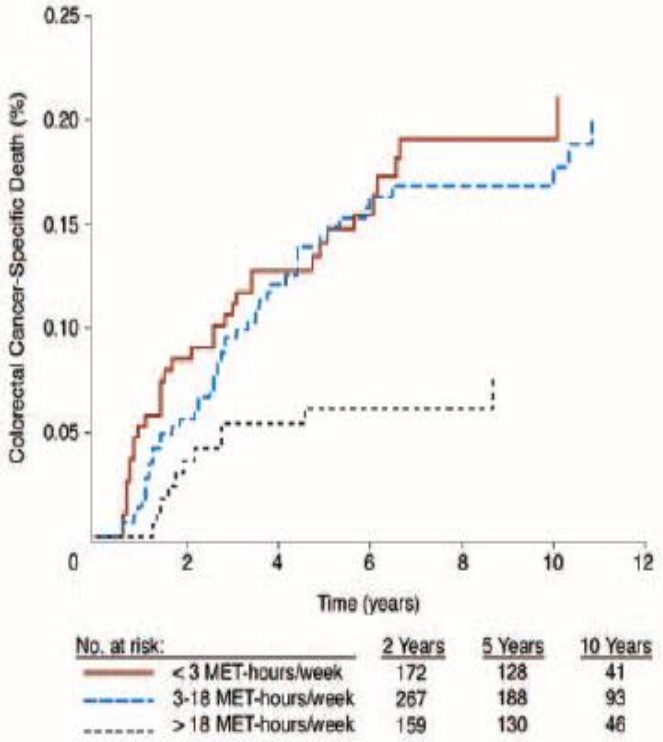
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Physical Activity and Survival After Colorectal Cancer Diagnosis

Jeffrey A. Meyerhardt, Edward L. Giovannucci, Michelle D. Holmes, Andrew T. Chan, Jennifer A. Chan, Graham A. Colditz, and Charles S. Fuchs

Prospective observational study of 573 women (stage I-III)



Cancer-specific mortality: HR 0.39 (0.18 – 0.82) ≥ 18 M-h/wk
Overall mortality: HR 0.43 (0.25 – 0.74) ≥ 18 M-h/wk

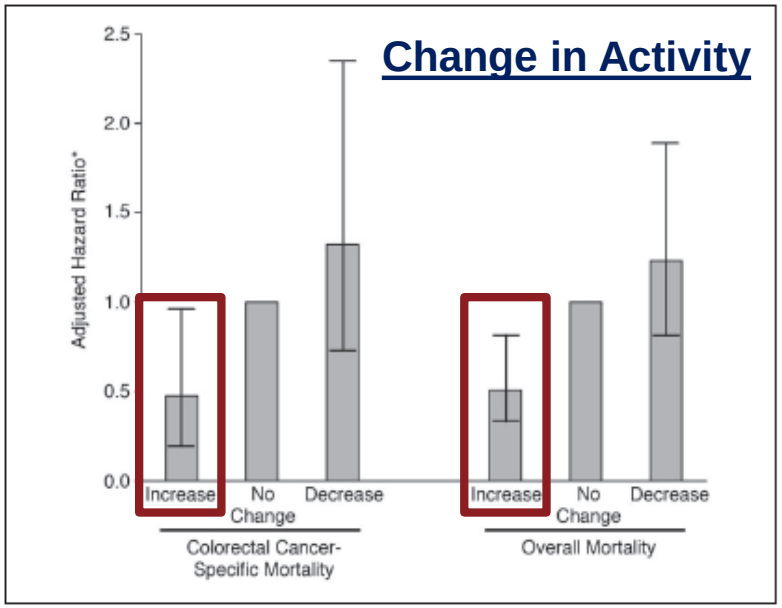


Fig 3. Impact of change of physical activity before and after colorectal cancer diagnosis. *Compared with no change. Adjusted for body mass index, stage of disease (I, II, III), grade of tumor differentiation, colon or rectal primary, age at diagnosis, year of diagnosis, receipt of chemotherapy (yes, no, unknown), time from diagnosis to physical activity measurement, change in body mass index, smoking status (current, past, never).

J Clin Oncol 24:3527-3534, 2006

VOLUME 24 · NUMBER 22 · AUGUST 1 2006

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Cancer Survival: Time to Get Moving? Data Accumulate Suggesting a Link Between Physical Activity and Cancer Survival

Wendy Demark-Wahnefried, *School of Nursing and Department of Surgery, Duke University Medical Center, Durham, NC*

Data from these three ***observational studies suggest a reduced risk of recurrence of 50% to 60%. Such an effect parallels that of trastuzumab (herceptin) for HER-2–positive breast cancer patients****, an agent heralded by the oncologic care community and by the Director of the National Cancer Institute, Andrew C. von Eschenbach, MD,* ***as "a major advance and turning point in eliminating suffering and death from cancer."***

© 2006 by American Society of Clinical Oncology

Exercise and Prostate Cancer Survival

VOLUME 29 · NUMBER 6 · FEBRUARY 20 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

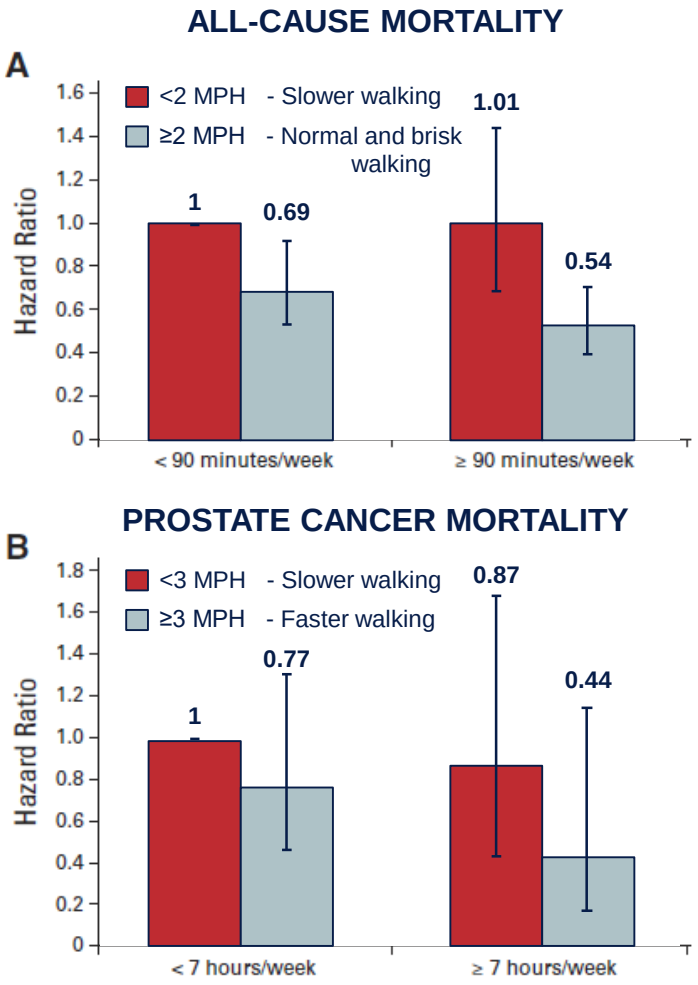
Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study

Stacey A. Kenfield, Meir J. Stampfer, Edward Giovannucci, and June M. Chan

N = 2,705, activity after diagnosis from 1990-2008 548 deaths, 112 result of PCa

≥3 hours per week of **vigorous** activity (biking, tennis, jogging, swimming) after diagnosis:

- 49% lower risk of all-cause mortality [HR, 0.51 (0.36 – 0.72)]
- 61% lower risk of prostate cancer mortality [HR, 0.39 (0.18 – 0.84)]



J Clin Oncol. 2011;29(6):726-732.

VOLUME 29 · NUMBER 21 · JULY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Exercise Behavior, Functional Capacity, and Survival in Adults With Malignant Recurrent Glioma

Emily Ruden, David A. Reardon, April D. Coan, James E. Herndon II, Whitney E. Hornsby, Miranda West, Diane R. Fels, Annick Desjardins, James J. Vredenburgh, Emily Waner, Allan H. Friedman, Henry S. Friedman, Katherine B. Peters, and Lee W. Jones

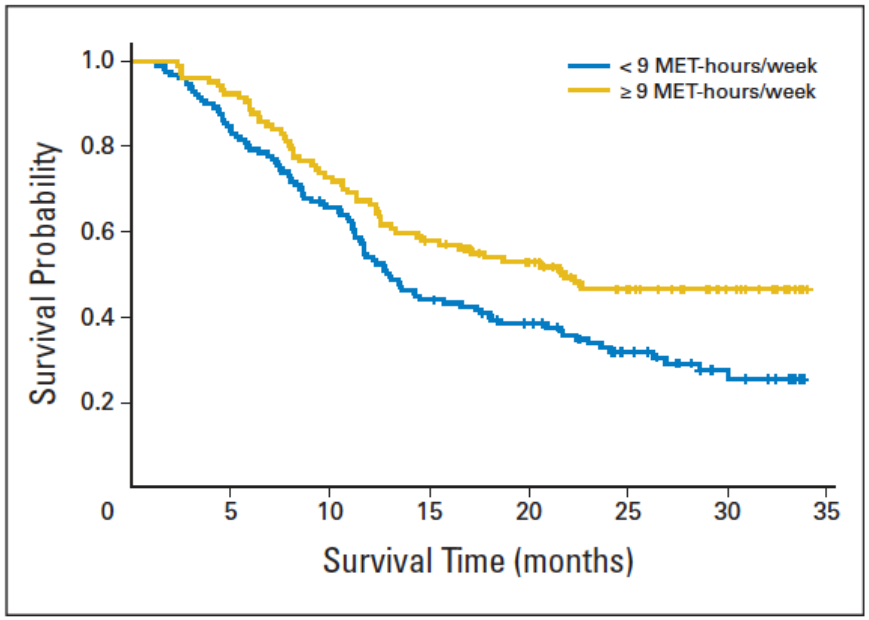


Fig 2. Association between exercise behavior (metabolic equaivalent [MET]–h/wk) and survival.

Prospective study in 243 patients with KPS ≥ 70

Aged 20-77 years
68% men
Godin Leisure-Time Exercise Questionnaire

Median survival:
13 months < 9 MET-h/wk
22 months ≥ 9 MET-h/wk

HR: 0.64 (0.46 – 0.91)

J Clin Oncol 29:2918-2923. © 2011

Exercise and Prostate Cancer Survival

Published OnlineFirst December 19, 2014; DOI: 10.1158/1055-9965.EPI-14-0707

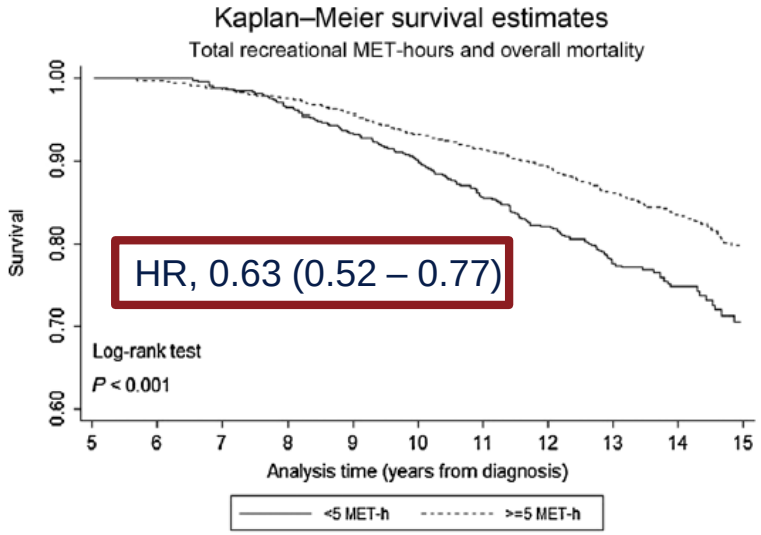
Research Article

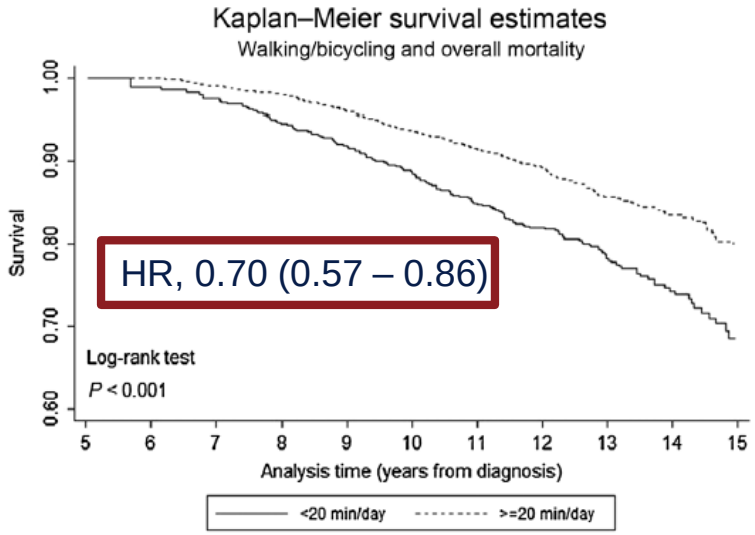
Cancer Epidemiology, Biomarkers & Prevention

Physical Activity and Survival among Men Diagnosed with Prostate Cancer

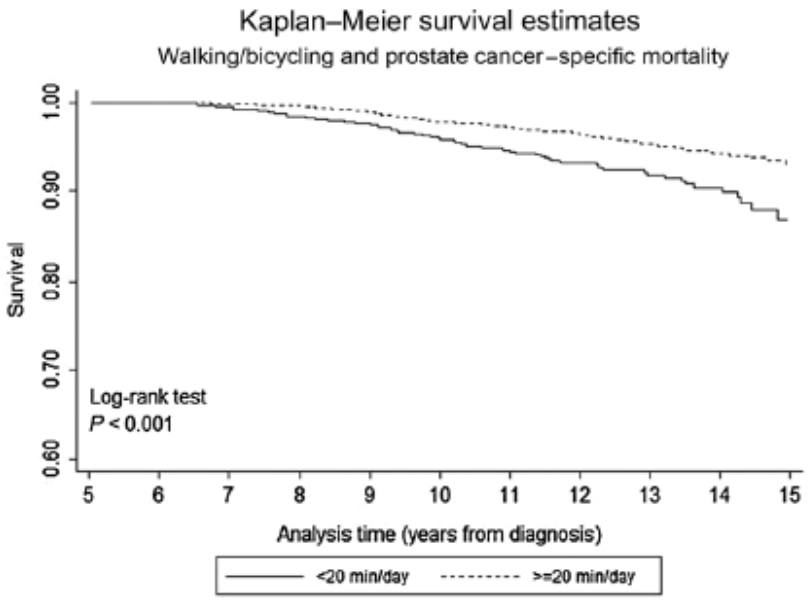
Stephanie E. Bonn[1], Arvid Sjölander[1], Ylva Trolle Lagerros[2], Fredrik Wiklund[1], Pär Stattin[3], Erik Holmberg[4], Henrik Grönberg[1], and Katarina Bälter[1]

4,623 men with localised PCa 1997-2002 followed-up until 2012
Post-diagnosis activity, 561 deaths with 194 from PCa

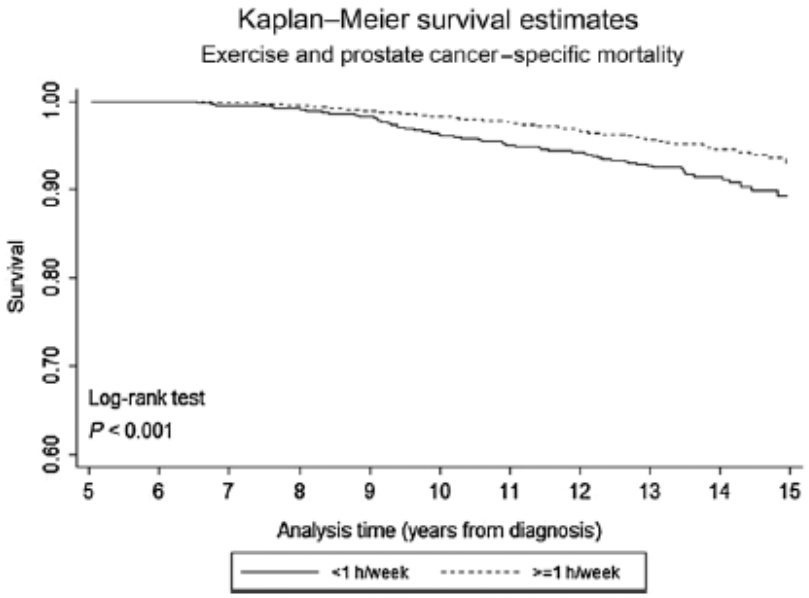




Bonn SE et al. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):57-64.



HR, 0.61 (0.43 – 0.87)



HR, 0.68 (0.48 – 0.94)

Bonn SE et al. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):57-64.

Exercise and Prostate Cancer Survival

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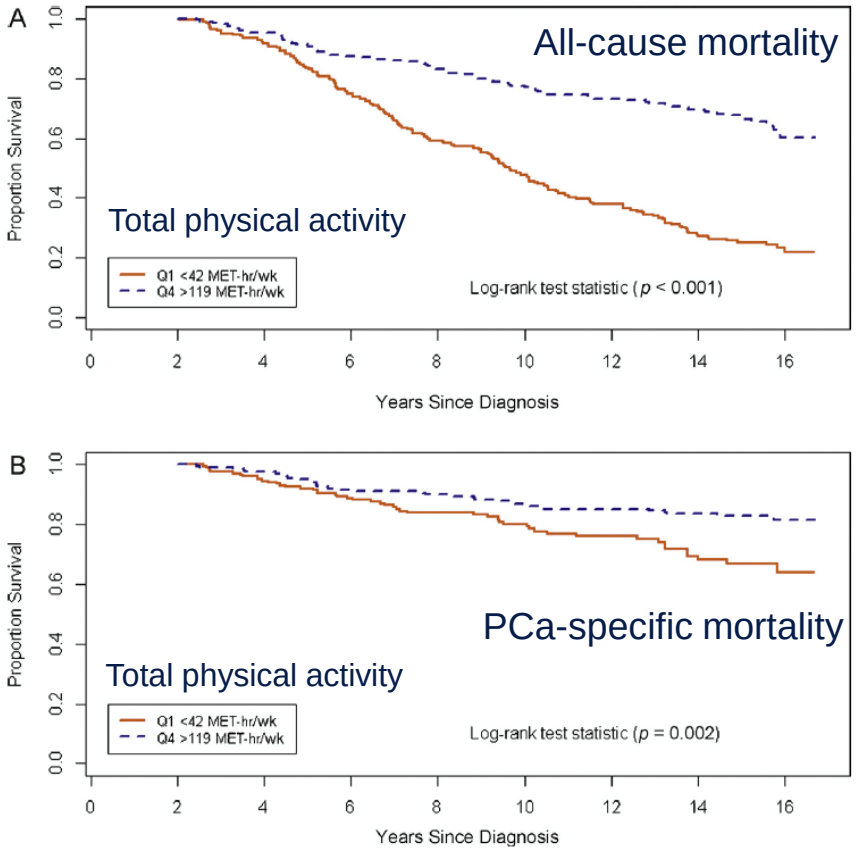
Physical Activity and Survival After Prostate Cancer

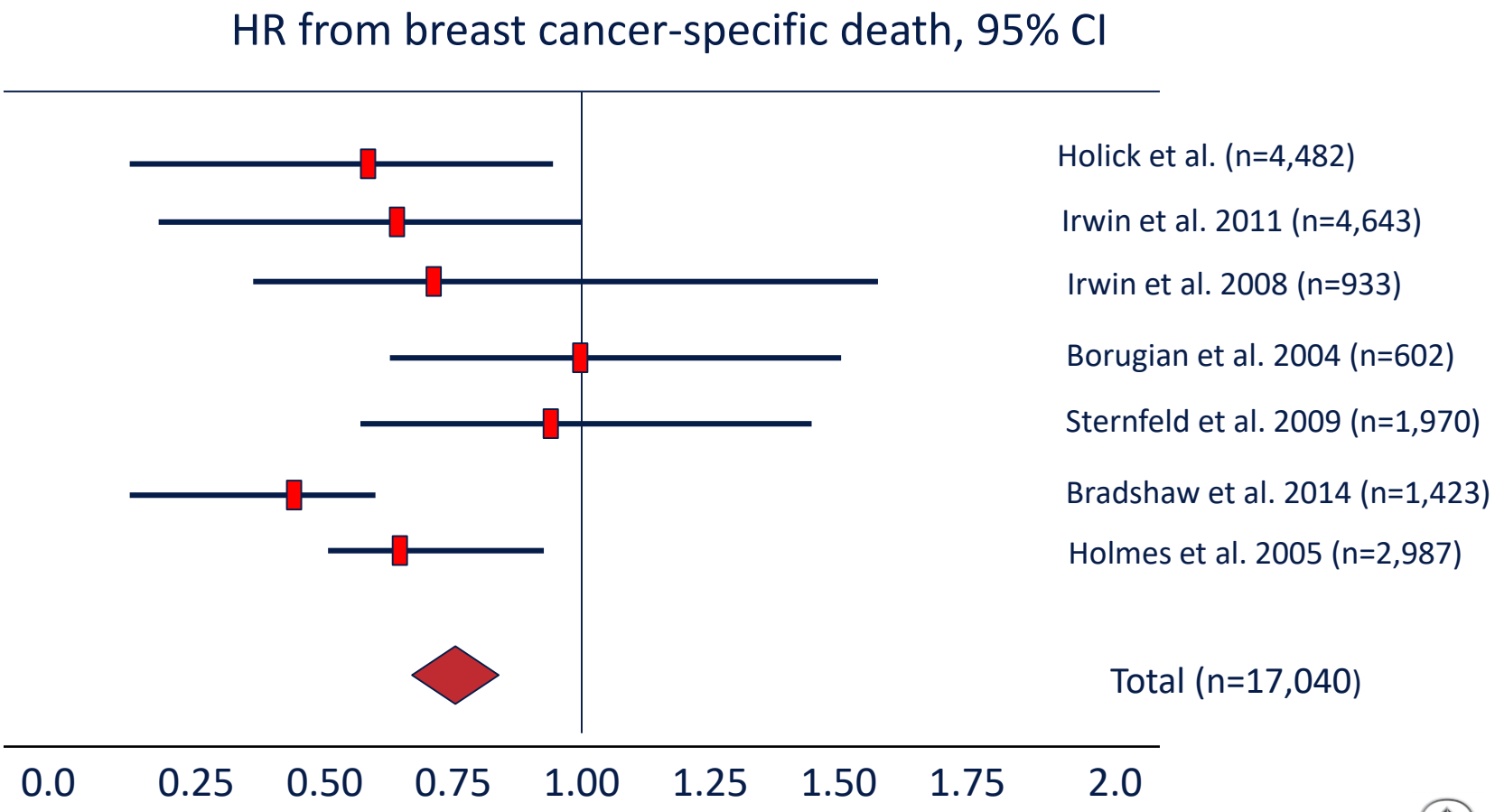
Christine M. Friedenreich[a,b,c,], Qinggang Wang[a], Heather K. Neilson[a], Karen A. Kopciuk[a,b,d], S. Elizabeth McGregor[b,c,e], Kerry S. Courneya[f]*



- 830 men with stage II-IV PCa between 1997-2000 with follow-up to 2014 (458 deaths, 170 PCa-specific)
- post-diagnosis recreational activity was associated with a significantly lower PCSM risk [**HR 0.56** (0.35 – 0.90)]
- sustained physical activity (pre and post) was associated with overall survival [**HR 0.66** (0.49 – 0.88)]

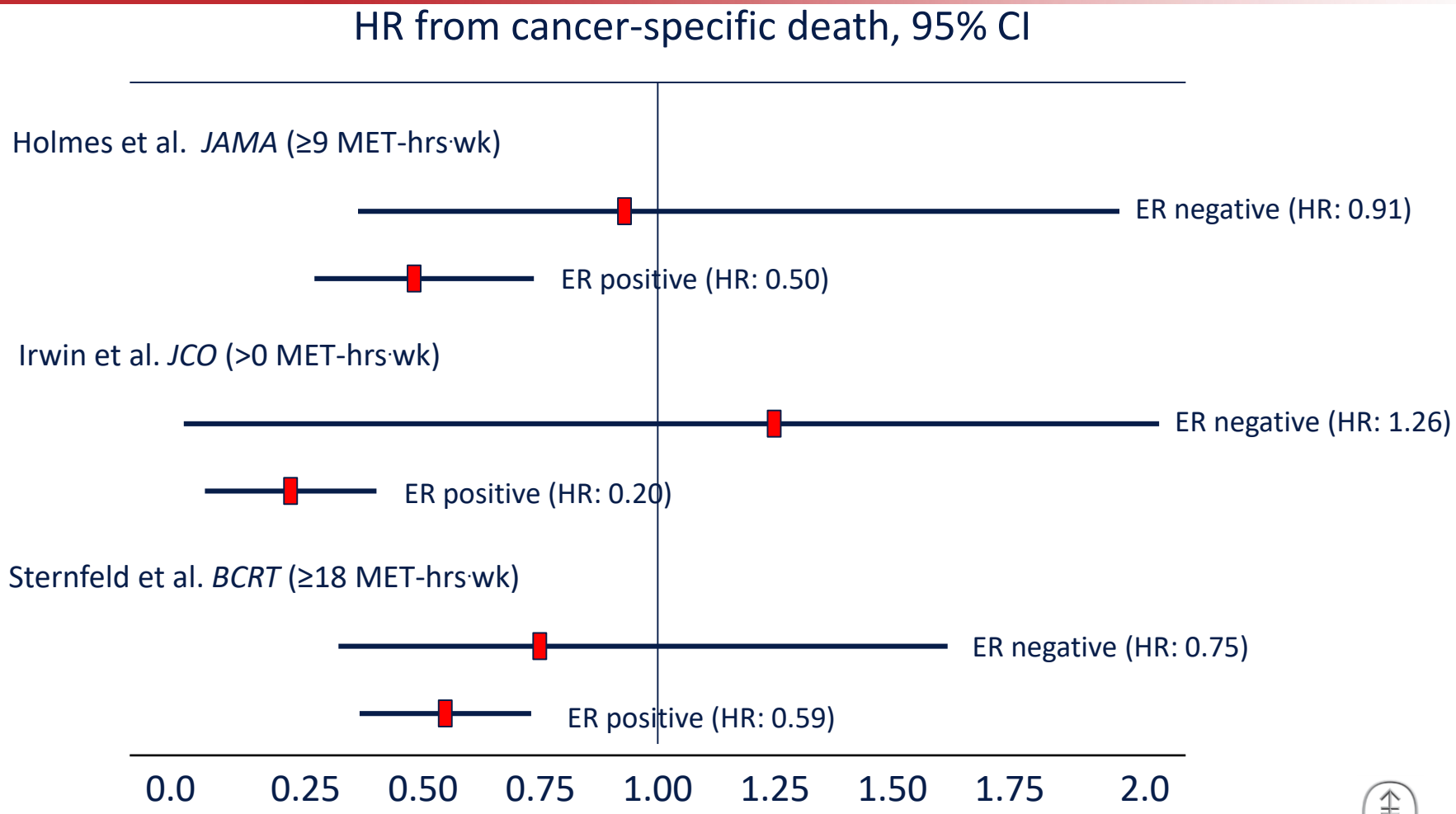
Eur Urol. Epub 2016 Jan 7.

Exercise and Breast Cancer Survival



Betof et al. *Brain Behav Immun*, 2013; Ballard-Barbash et al. *JNCI*, 2013

Exercise and cancer outcomes: Impact of ER status



Physical activity and survival among long-term cancer survivor and non-cancer cohorts

Anthony Gunnell[1, 2], Sarah Joyce[3], Stephania Tomlin[3], Dennis R. Taaffe[1, 4, 5], Prue Cormie[6], Robert U. Newton[1, 7, 4], David Joseph[1, 8], Nigel Spry[1, 9], Kristjana Einarsdóttir[10], Daniel A. Galvao[1, 4*]

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frontiers in Public Health

N=1589 Western Australian Cancer Survivors; 8.8 years follow-up
Cox proportional hazards regression

	Cancer Specific Death
<150 minutes	HR 0.62 (0.36-1.06)
150-359 minutes	HR 0.55 (0.28-1.08)
360+ minutes	**HR 0.30** (0.13-0.70)

	All-Cause Death
<150 minutes	HR 0.70 (0.46-1.08)
150-359 minutes	**HR 0.55 (0.31-0.97)**
360+ minutes	**HR 0.30 (0.21-0.79)**

Gunnell et al. Frontiers Public Health 2017

Resistance Exercise and Cancer Survival

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MAYO CLINIC

ORIGINAL ARTICLE

The Effect of Resistance Exercise on All-Cause Mortality in Cancer Survivors

Justin P. Hardee, MS; Ryan R. Porter, MS; Xuemei Sui, MD, MPH, PhD; Edward Archer, PhD; I-Min Lee, MD, ScD; Carl J. Lavie, MD; and Steven N. Blair, PED

- 2863 cancer survivors enrolled in the Aerobics Center Longitudinal Study
- RE was associated with a 33% lower risk of all-cause mortality (95% CI, 0.45-0.99) after adjusting for potential confounders, including PA

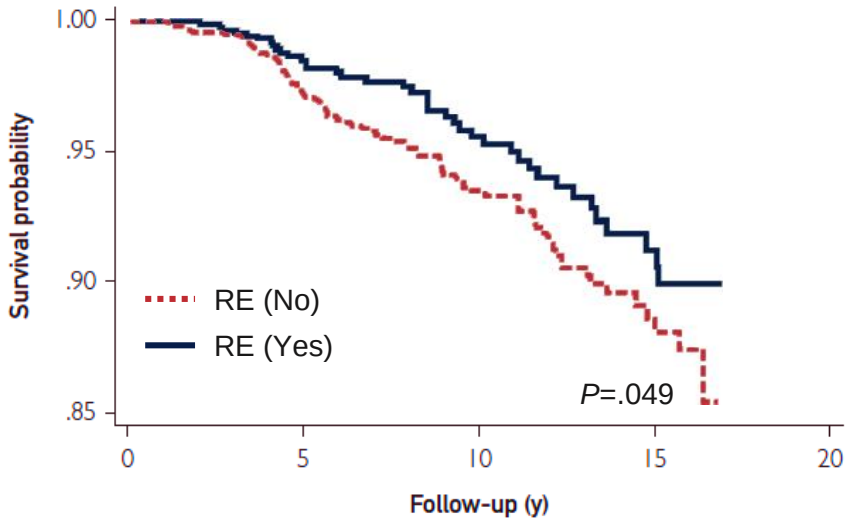

Figure 1. Kaplan-Meier survival curves for all-cause mortality according to RE performed at least 1 day/week in cancer survivors enrolled in the Aerobics Center Longitudinal Study, Dallas, Texas, 1987 to 2003.

PA, physical activity; RE, resistance exercise.

Hardee JP et al. *Mayo Clin Proc*. 2014;89(8):1108-1115.

Observational Studies: Exercise and Cancer Survival?

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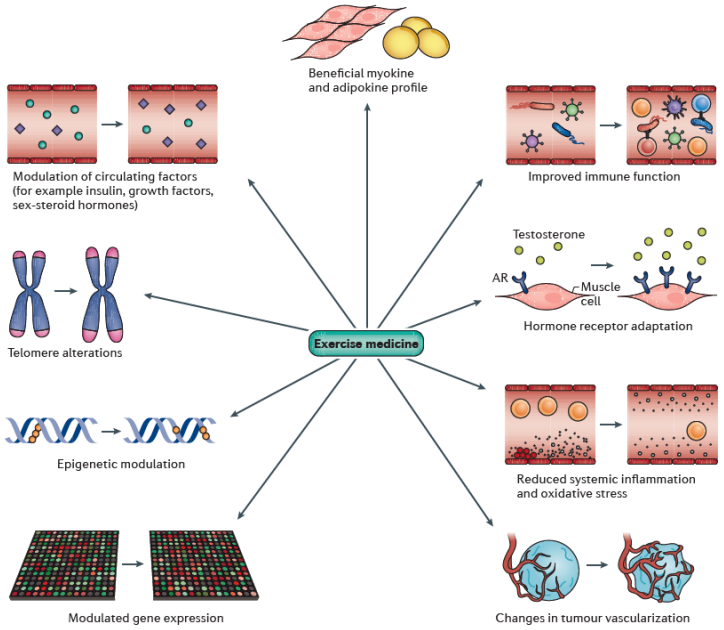
Limitations:

- Self-report of physical activity/exercise
- Reverse causation bias
- Association vs. cause and effect

Causal criteria of Hill:

- ✓ Strength
- ✓ Consistency (replicated)
- ✓ Biological gradient
- ✓ Plausibility



Hill BA. Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial

Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, and Donald C. McKenzie

START trial - Multicenter

RCT 24 weeks exercise intervention (different modes)

n=242 breast cancer survivors initiating chemotherapy (median 17 weeks)

78 (71) assigned to aerobic exercise
56 received intervention
22 did not complete ≥ 66% of supervised exercise

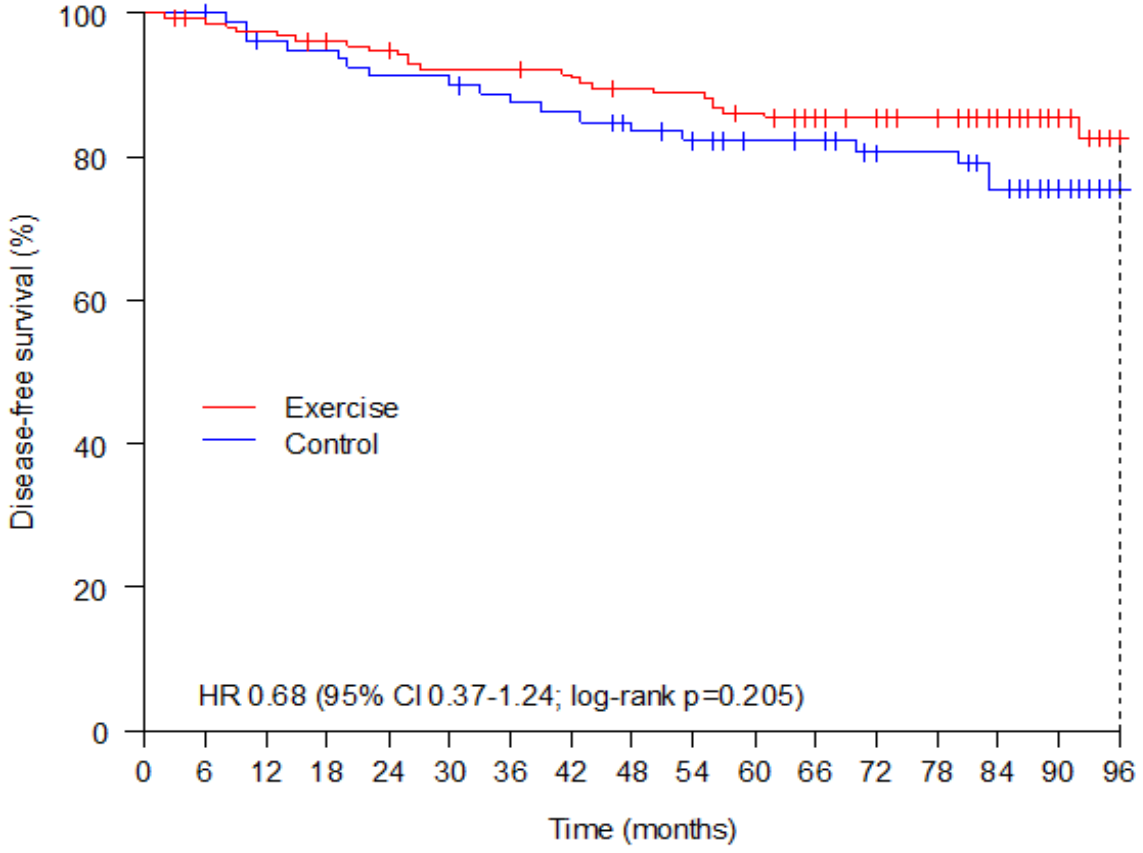
82 (73) assigned to resistance exercise
56 received intervention
26 did not complete ≥ 66% of supervised exercise

82 (75) assigned to usual care
82 received intervention

Courneya et al. *JCO* 2007;25:4396-4404

Disease-Free Survival

8-year DFS was 82.7% for EX vs. 75.6% for UC



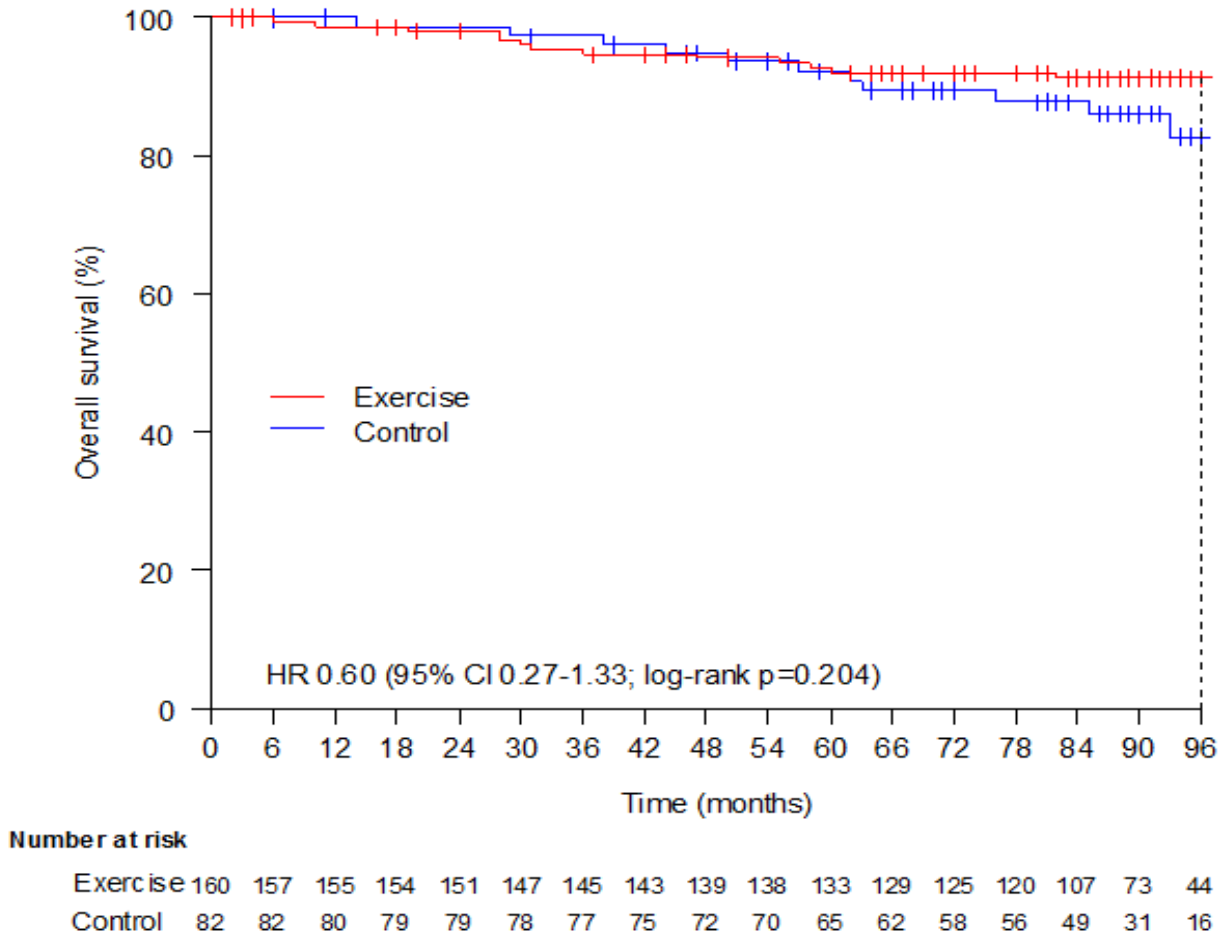
Number at risk

Exercise	160	156	153	150	146	140	140	138	133	131	124	120	116	111	99	67	39
Control	82	82	77	76	73	73	70	67	64	61	57	56	51	50	42	25	13

Courneya et al. *MSSE* 2014;46:1744-51

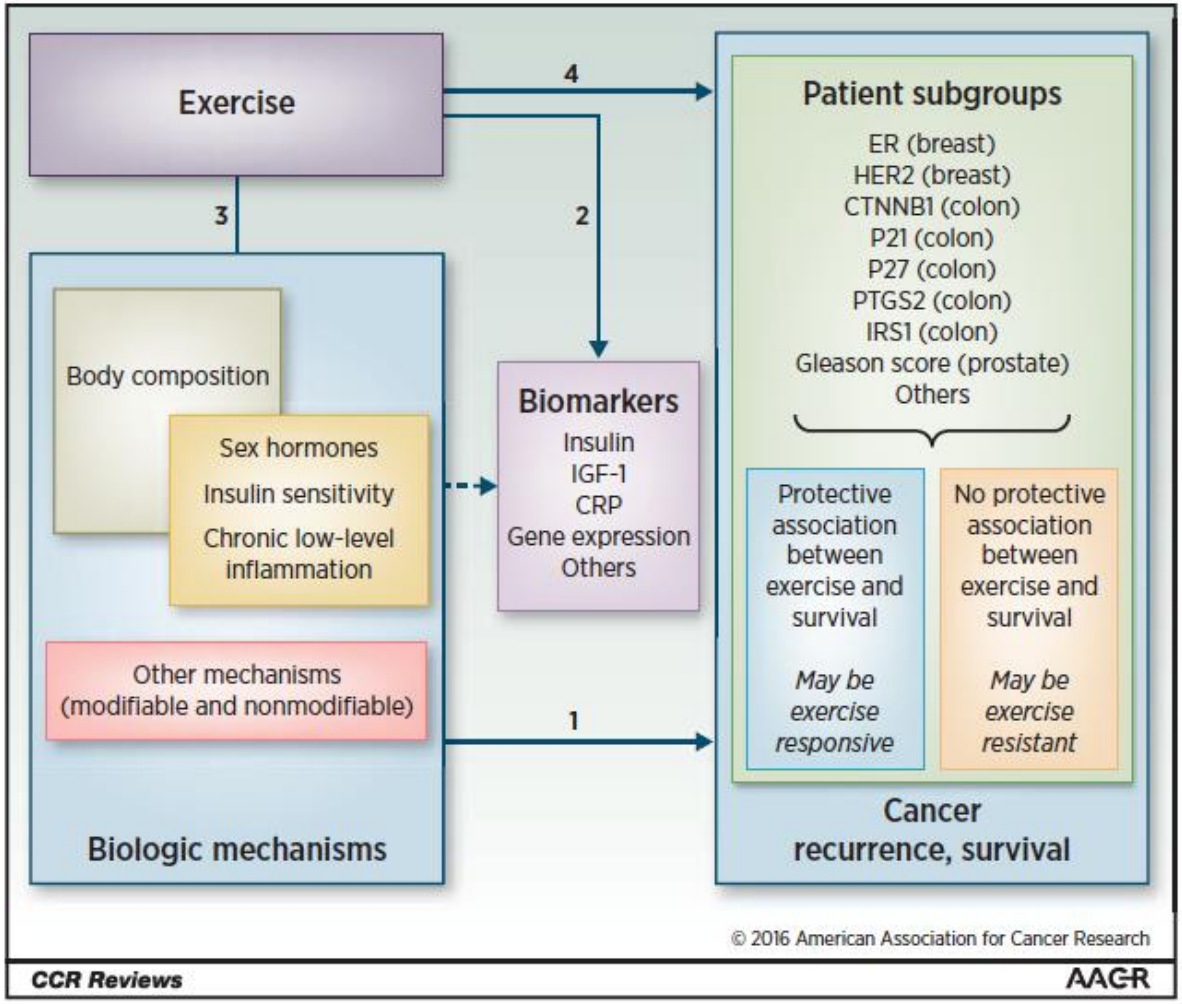
Overall Survival

8-year OS was 91.2% for EX vs. 82.7% for UC



Courneya et al. *MSSE* 2014;46:1744-51

Physical Activity and Cancer Outcomes: A Precision Medicine Approach



Friedenreich et al. Clin Cancer Res. 2016 Jul 12.

Definitive Trials

The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group

K.S. Courneya PhD, C.M. Booth MD,† S. Gill MD,‡ P. O'Brien MSc,† J. Vardy MD PhD,§ C.M. Friedenreich PhD,|| H.J. Au MD,# M.D. Brundage MD,† D. Tu PhD,† H. Dhillon MA,§ and R.M. Meyer MD†*

Movember funded, Global Action Plan (GAP4): ***INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-MCRPC): a multi-centre randomised controlled phase III study***.

Platinum Priority – Editorial
Referring to the article published on pp. x–y of this issue

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Accumulating Evidence for Physical Activity and Prostate Cancer Survival: Time for a Definitive Trial of Exercise Medicine?

Robert U. Newton *, *Daniel A. Galvão*

Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia

INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – mCRPC)

Multicentre, randomised, controlled phase III trial evaluating highly specific anabolic and aerobic exercise prescription tailored for men with metastatic castrate-resistant prostate cancer with the primary outcome being overall survival

866 men with mCRPC, 24 month intervention

Elucidate mechanisms by which exercise delays cancer progression

Jointly led by ECU and UCSF

Protocol presented at ASCO 2016 Saad et al.

National/international Sites

INTERVAL – mCRPC

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Investigator Sites

1.	Edith Cowan University - WA, AUS. - Open for Recruitment
2.	Deakin University - VIC, AUS.
3.	Queensland Consortium - QLD, AUS.
4.	Orange Base Hospital - NSW, AUS.
6.	Auckland University of Technology - NZ.
7.	University of California, San Francisco - USA.
8.	Ohio State Health University - USA.
9.	University of Washington - USA.
10.	Cedars-Sinai Medical Centre - USA.
11.	Fred Hutchison Cancer Centre - USA.
12.	University of Colorado, Denver – USA.
13.	University of Alberta - Canada. Open for Recruitment
14.	University of Montreal Hospital Centre - Canada.
15.	Princess Margaret Cancer Center - Canada.
16.	Kings College, London - UK.
17.	University of Surrey - UK.
18.	University of Bristol - UK.
19.	University of Oxford - UK.
20.	University of Glasgow - UK.
21.	Trinity College, Dublin - IRE.
22.	German Sports University - GER. Open for Recruitment
23.	Erasmus Medical Centre – ND.

Summary/Conclusions

- Self-reported PA/exercise behavior is associated with survival in several cancer groups (breast, colon, prostate)
- Phase II data suggestive of possible survival benefit of supervised exercise in breast cancer
- Phase III exercise trials ongoing in colon and prostate cancer

Research Support

Robert Newton (ECU)
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Thomas Shannon (HH)
James Denham (UNew, NMH)
David Lamb (UOtago)
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Akhlil Hamid (PRH, ECU)
Evan Ng (RPH, Genesis)
Raphael Chee (Genesis, UWA)
Jerard Ghossein (JHC)
Siobhan Ng (SCGH, SJG)
Yvonne Zissiadis (Genesis, ECU)

Prostate Cancer Foundation of Australia

Australian Government
National Health and Medical Research Council
NHMRC

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Cancer Council Western Australia

Australian Government
Cancer Australia

Cancer Council Queensland

abbvie

Australian Government
Department of Innovation, Industry, Science and Research

beyondblue
the national depression initiative

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Thank You!

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Prospective Cohort Studies of Post Diagnosis Exercise and Cancer-Specific Mortality

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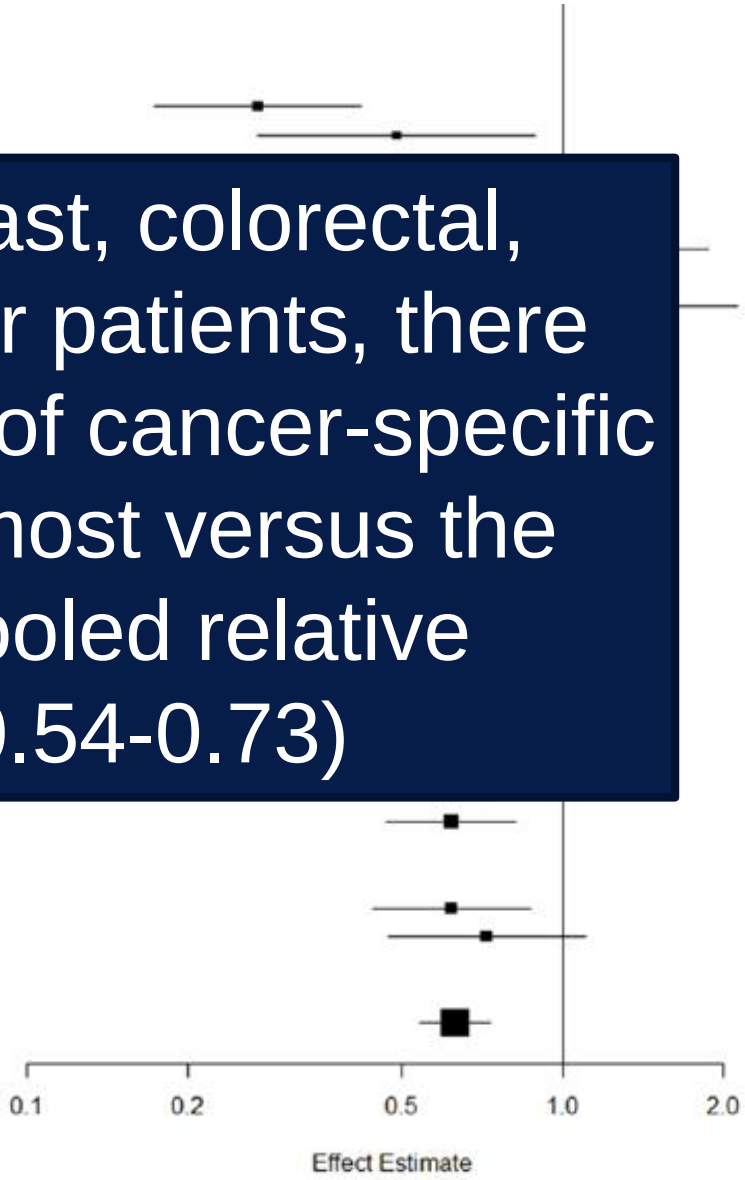
Author, year	No. Events/Cases	Effect Estimate	95% CI
Breast			
Bradshaw, 2014 (10)	195/1,033	0.27	0.17-0.42
Holick, 2008 (26)	109/4,482	0.49	0.27-0.89
Borch			
Holm			
Irwin,			
Irwin,			
Willia			
de G			
Stern			
Boru			
Poole			
Colo			
Kuipe			
Meye			
Meye			
Arem			
Camp			
Baad			
Poole			
Pros			
Kenfi			
Fried			
Bonn			
Pooled Estimate (I^2=0.8%)	476/8,158	0.62	0.47-0.82
Any			
Lee, 2014 (20)	337/1,021	0.62	0.44-0.87
Inoue-Choi, 2013 (21)	184/2,017	0.72	0.47-1.10
Overall			
Pooled Estimate (I^2=47.9%)	3,307/38,560	0.63	0.54-0.73

Across 24 studies of breast, colorectal, prostate, and mixed cancer patients, there was a 37% reduction in risk of cancer-specific mortality, comparing the most versus the least active patients (pooled relative risk=0.63, 95% CI: 0.54-0.73)



Friedenreich et al., *Clin Cancer Res*. 2016;22:4766-4775.

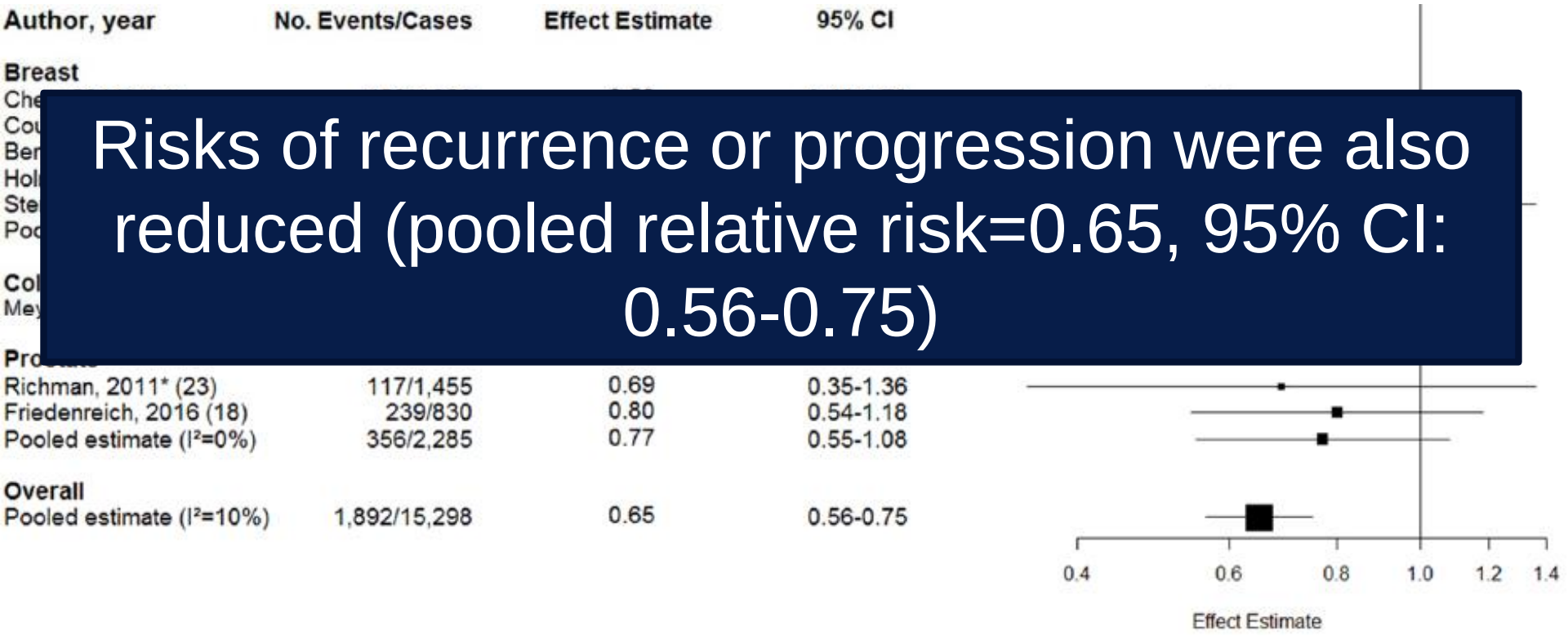
Prospective Cohort Studies of Post Diagnosis Exercise and Cancer Recurrence and Progression

Exercise Medicine Research Institute

VARIO health clinic

ECU AUSTRALIA EDITH COWAN UNIVERSITY

Risks of recurrence or progression were also reduced (pooled relative risk=0.65, 95% CI: 0.56-0.75)



Friedenreich et al., *Clin Cancer Res*. 2016;22:4766-4775.

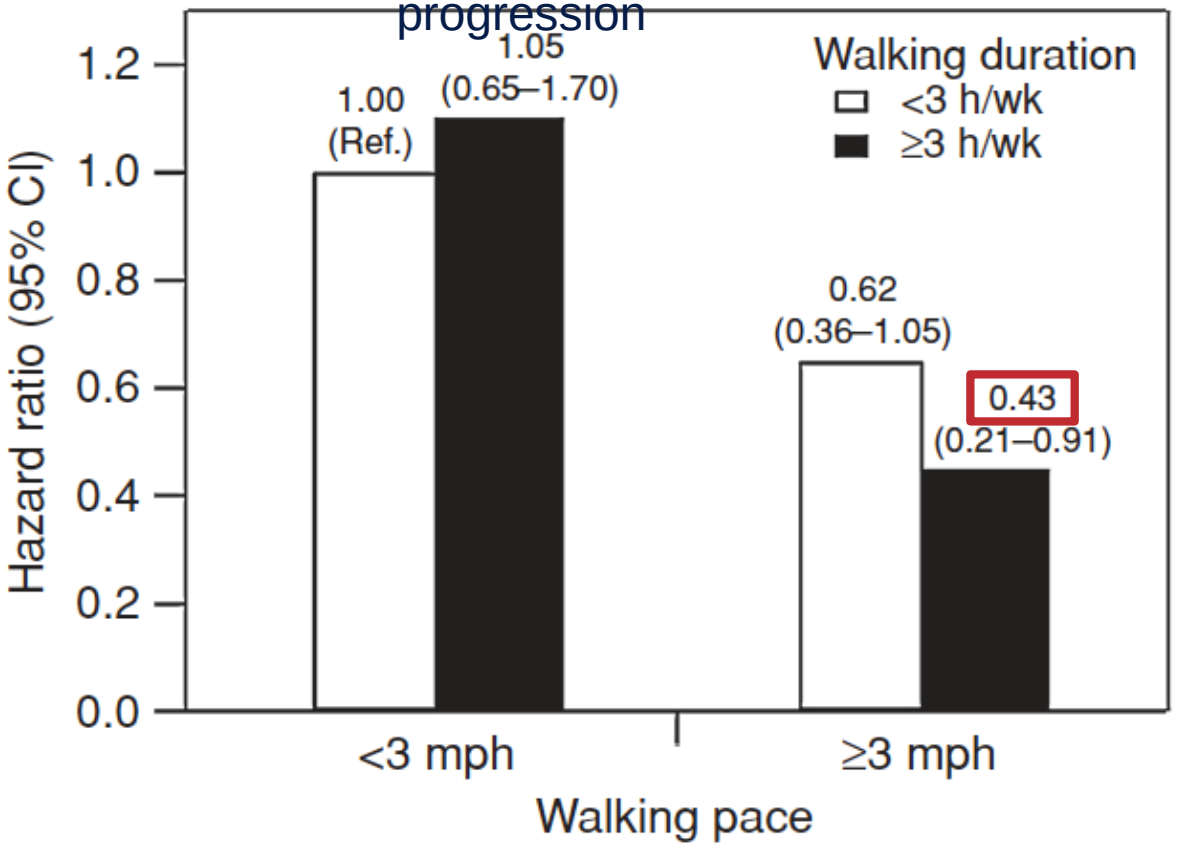
Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor

Erin L. Richman[1,2,4], Stacey A. Kenfield[1,3], Meir J. Stampfer[1,2,3], Alan Paciorek[4], Peter R. Carroll[4,6], and June M. Chan[4,5,6]

Cancer Res; 71(11); 3889–95. ©2011 AACR.

57% lower PCa progression

Postdiagnostic walking duration, walking pace, and risk of PCa progression among **1,455 men** diagnosed with clinically local PCa



Colon Health and Life-Long Exercise Change (CHALLENGE) Trial

Exercise Medicine Research Institute

VARIO health clinic

AUSTRALIA ECU EDITH COWAN UNIVERSITY

- RCT comparing 3 year PA intervention to CON on disease-free survival in colon cancer survivors 2-6 months after treatment.
- first exercise trial with survival outcome as primary endpoint.
- multinational trial with 962 planned participants.
- trial opened to accrual in May 2009.
- funded by NCIC-CTG and NHMRC in Australia.

What Are MET Hours?

- Each activity is assigned a MET score
- 1 MET is the energy expenditure for sitting quietly
- MET scores are the ratio of the metabolic rate for the activity / resting metabolic rate
- MET-hours/week for each activity calculated from the reported hours per week for that activity x assigned MET score
- Values from individual activities summed for a total of MET-hours/week

Table 1. MET-Hours of Activities Surveyed

Leisure-Time Activity	MET-Hours
Normal pace walking (2 to 2.9 mph)	3
Brisk pace walking (3 to 3.9 mph)	4
Very brisk pace walking (4+ mph)	4.5
Jogging (slower than 10 min/mile)	7
Running (faster than 10 min/mile)	12
Bicycling	7
Tennis, squash, racquetball	7
Lap swimming	7
Calisthenics, ski or stair machine, other aerobic exercise	6
Yoga, stretching, toning, lower intensity exercise	4
Other vigorous activities (lawn mowing)	6

Abbreviations: MET, metabolic equivalent task; mph, miles per hour.

Walking at Average Pace

< 3 MET-h/wk = < 1 hr/wk

3-9 MET-h/wk = 1-3 hr/wk

9-18 MET-h/wk = 3-6 hr/wk