Overview of the Evidence on Cancer Outcomes Related to Physical Activity (PA)

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Overview of the Talk

- systematic review of PA and cancer outcomes.
- biologic mechanisms and precision medicine approach.
- limitations of research into PA and cancer outcomes.
- ongoing studies of PA and cancer outcomes.
- summary and conclusions.

Review

Clinical Cancer Research

Physical Activity and Cancer Outcomes: A Precision Medicine Approach

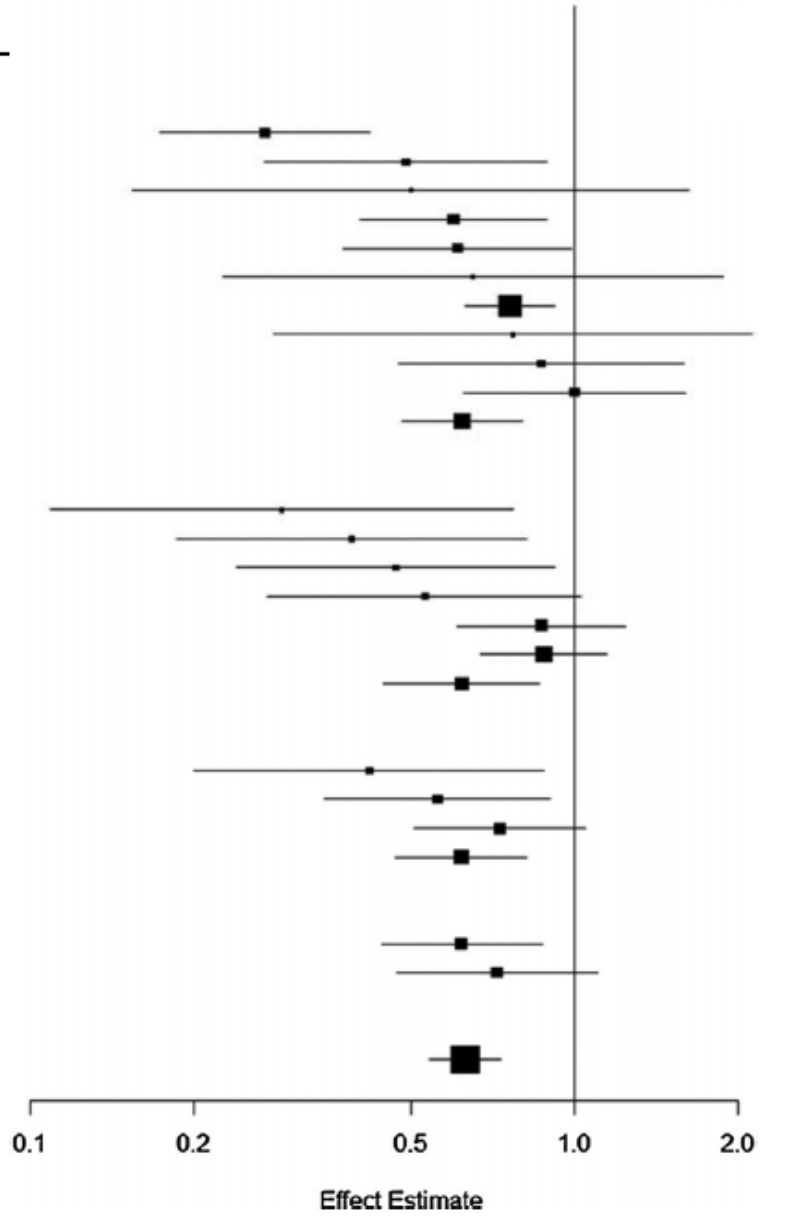
CME

Christine M. Friedenreich[1,2,3], Heather K. Neilson[1], Megan S. Farris[1,3], and Kerry S. Courneya[4]

(Friedenreich et al. *Clin Can Res* 2016;22:4766-75)

Table 1. Individual and pooled risk estimates from prospective cohort studies that related postdiagnosis physical activity to cancer-specific mortality, by cancer site

Author, year	No. of 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, 2015 (9)	155/1,327	0.50	0.15–1.62
Holmes, 2005 (27)	280/2,987	0.60	0.40–0.89
Irwin, 2011 (11)	86/2,910	0.61	0.38–0.99
Irwin, 2008 (28)	115/933	0.65	0.23–1.87
Williams, 2014 (8)	46/986	0.76	0.63–0.92
de Glas, 2014 (12)	39/435	0.77	0.28–2.12
Sternfield, 2009 (29)	102/1,970	0.87	0.48–1.59
Borugian, 2004 (7)	112/603	1.00	0.63–1.60
Pooled Estimate ($I^2 = 61.3\%$)	1,239/17,666	0.62	0.48–0.80
Colorectal			
Kuiper, 2012 (13)	51/606	0.29	0.11–0.77
Meyerhardt, 2006 (30)	80/573	0.39	0.19–0.82
Meyerhardt, 2009 (31)	88/661	0.47	0.24–0.92
Arem, 2015 (14)	128/3,797	0.53	0.27–1.03
Campbell, 2013 (15)	379/2,236	0.87	0.61–1.24
Baade, 2011 (16)	345/1,825	0.88	0.67–1.15
Pooled Estimate ($I^2 = 56.6\%$)	1,071/9,698	0.62	0.45–0.86
Prostate			
Kenfield, 2011 (17)	112/2,705	0.42	0.20–0.88
Friedenreich, 2016 (18)	170/830	0.56	0.35–0.90
Bonn, 2015 (19)	194/4,623	0.73	0.51–1.05
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



(Friedenreich et al. *Clin Can Res* 2016;22:4766-75)

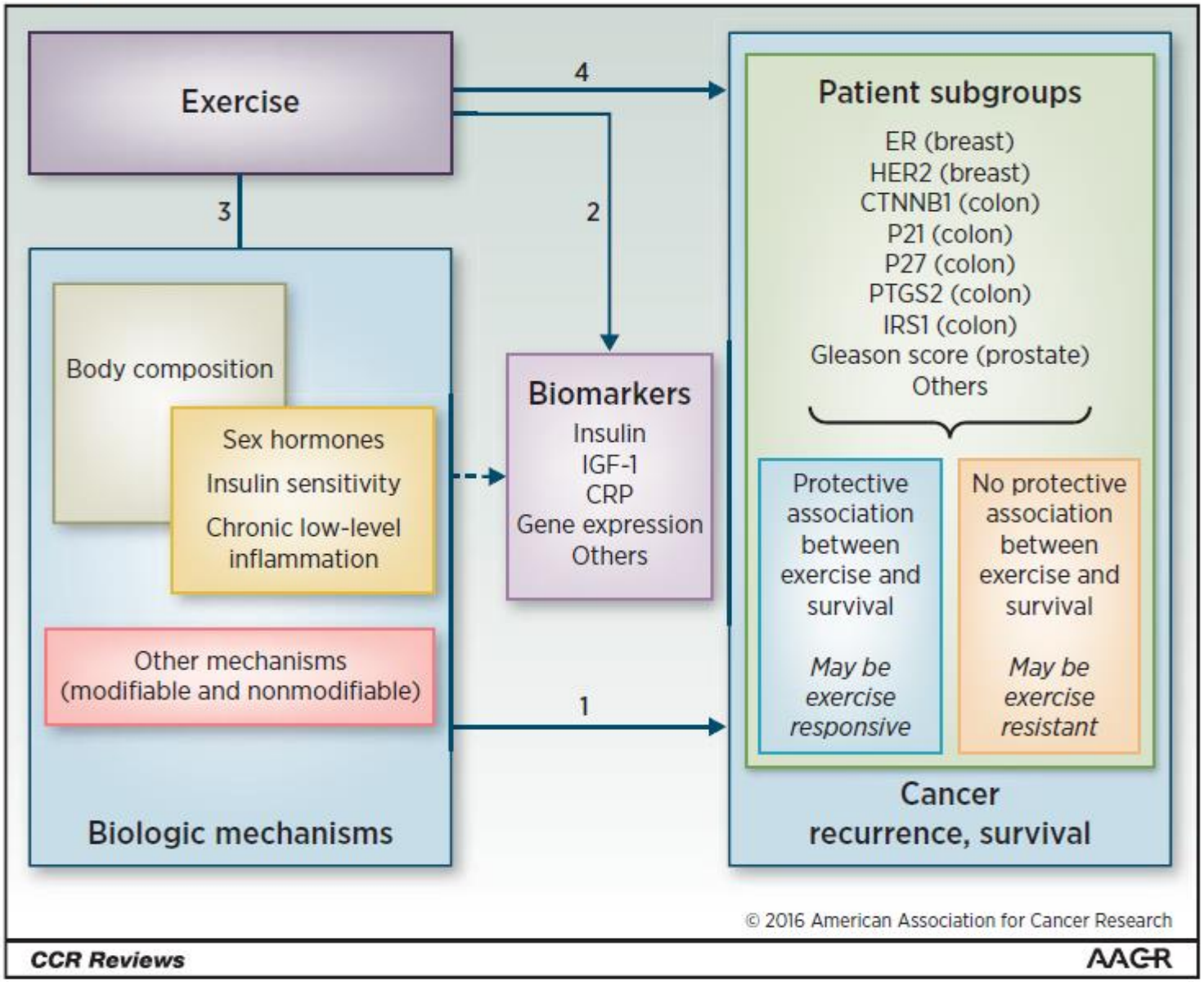
Table 1 Mainly direct biochemical changes related to exercise

Class of effect	Effector molecule or gene	Effect of exercise on effector molecule or gene
Cell growth regulators	IGF-1	Decreased levels[32–36]
	IGFBP3	Increased levels[35 36]
Proteins involved in DNA damage repair	BRCA1	Increased expression[41–44]
	BRCA2	Increased expression[41–44]
Androgen receptor coactivators	*RAS* family oncogenes	Suppressed activity[40]
Regulators of apoptosis and cell cycle arrest	P53	Enhanced activity[43–45]
	Heat shock proteins	Enhanced activity[55 61–66]
Hormonal systems	Oestrogen	Reduced activity[29 70 117 125–143]
	Testosterone	Transient rise then reduced activity[70–84]
	VIP	Transient rise then reduced activity[49 51–53]
	Leptin	Reduced activity[133 138–142 144]
	Irisin	Enhanced activity[85–90]
	Resistin	Reduced activity[123 124 145]
Immune system components	Natural killer cells	Enhanced activity[91–97]
	White cells	Enhanced activity[91–94]
Inflammation	C reactive protein, interleukin-6, TNFα	Reduced activity[93–102]
	Prostaglandins	Reduced activity[106–114]
	COX-2	Reduced activity[106–114]
Oxidative stress and antioxidant pathways	Glutathione, catalase and superoxide dismutase	Increased activity[55 57 59 60]

COX-2, cyclo-oxidase-2; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; TNF, tumour necrosis factor; VIP, vasoactive intestinal peptide.

(Thomas et al. *Brit J Sports Med* 2016;online)

Figure 1:



(Friedenreich et al. *Clin Can Res* 2016;22:4766-75)

Table 2. Subgroup analyses by molecular markers for colon cancer–specific mortality comparing high to low levels of physical activity

	Events/*n*	MET-hours/week ≥18 vs MET-hours/week <18; hazard ratio † (95% CI)	$P_{interaction}$
All patients with tumor blocks*	50/484	0.64 (0.33-1.23)	
FASN			0.77
Negative	41/390	0.61 (0.30-1.25)	
Positive	4/66	0.95 (0.11-8.06)	
K-ras			0.59
Wild-type	25/284	0.71 (0.28-1.82)	
Mutation	22/169	0.42 (0.15-1.18)	
p53			0.58
Negative	20/276	0.46 (0.16-1.35)	
Positive	26/192	0.64 (0.26-1.59)	
p21			0.19
Lost	37/360	0.87 (0.42-1.81)	
Expressed	8/90	0.10 (0.01-0.98)	
p27			0.03
Lost	17/195	1.40 (0.41-4.72)	
Expressed	28/251	0.32 (0.12-0.85)	
PI3KCA			0.96
Wild-type	33/340	0.59 (0.26-1.33)	
Mutation	7/69	1.25 (0.25-6.40)	

Abbreviations: *n*, total number of patients; CI, confidence interval.
*Block cohort represents subjects who had tumor blocks available, postdiagnosis physical activity data and stages I to III at diagnosis. The number of patients varies for each marker because some samples were indeterminant for certain markers.
†Adjusted for age, gender, stage, year of diagnosis, histology grade, BMI, and time of physical activity assessment.

(Meyerhardt et al. *Clin Can Res* 2009;15:5931-6)

Limitations of PA Research

- no randomized trials with survival endpoints.

For observational studies:

- none had PA/fitness as primary exposure.
- basic assessment of self-reported PA.
- no/crude measures of sedentary behavior (SB).
- no objective measures of PA or SB.

Limitations of PA Research

- no objective fitness assessments .
- limited biomarker data.
- few designed as cancer survivor cohorts.
- variable and arbitrary follow-up time points.
- limited disease and treatment data (covariates).
- few cancer groups have been examined.

Recent and Ongoing Studies

- follow-up of the START Trial (breast).
- update of the AMBER Cohort Study (breast).
- update of the CHALLENGE (CO.21) Trial (colon).
- update of the INTERVAL (GAP4) Trial (prostate).

EPIDEMIOLOGY

Effects of Exercise during Adjuvant Chemotherapy on Breast Cancer Outcomes

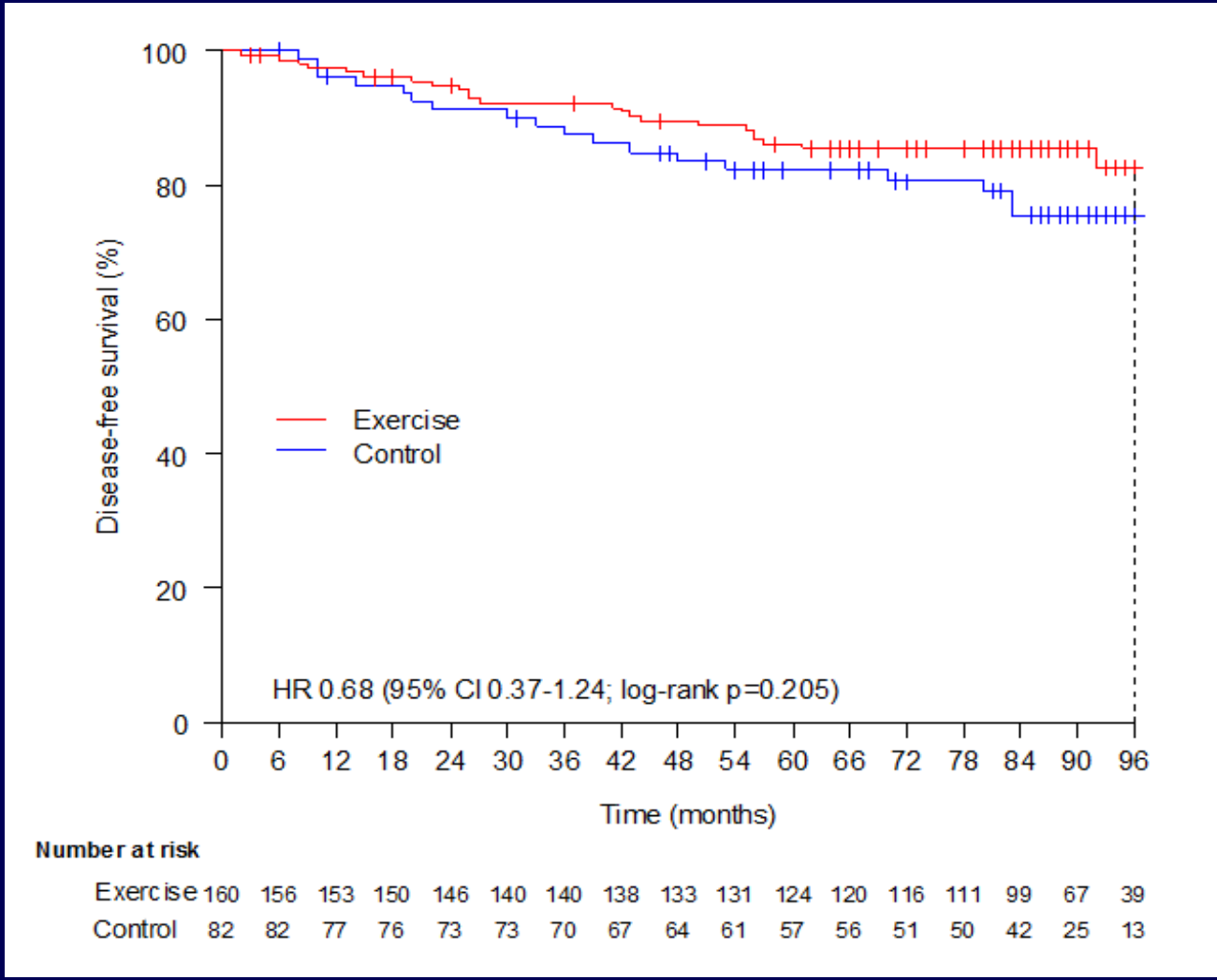
KERRY S. COURNEYA[1], ROANNE J. SEGAL[2], DONALD C. MCKENZIE[3], HUIRU DONG[1], KAREN GELMON[3,4], CHRISTINE M. FRIEDENREICH[5], YUTAKA YASUI[1], ROBERT D. REID[6], JENNIFER J. CRAWFORD[1], and JOHN R. MACKEY[1,7]

[1]Faculty of Physical Education, University of Alberta, Edmonton, Alberta, CANADA; [2]Ottawa Hospital Regional Cancer Center, Ottawa, Ontario, CANADA; [3]School of Kinesiology, University of British Columbia, Vancouver, British Columbia, CANADA; [4]British Columbia Cancer Agency, Vancouver, British Columbia, CANADA; [5]Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, CANADA; [6]University of Ottawa Heart Institute, Ottawa, Ontario, CANADA; and [7]Cross Cancer Institute, Edmonton, Alberta, CANADA

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

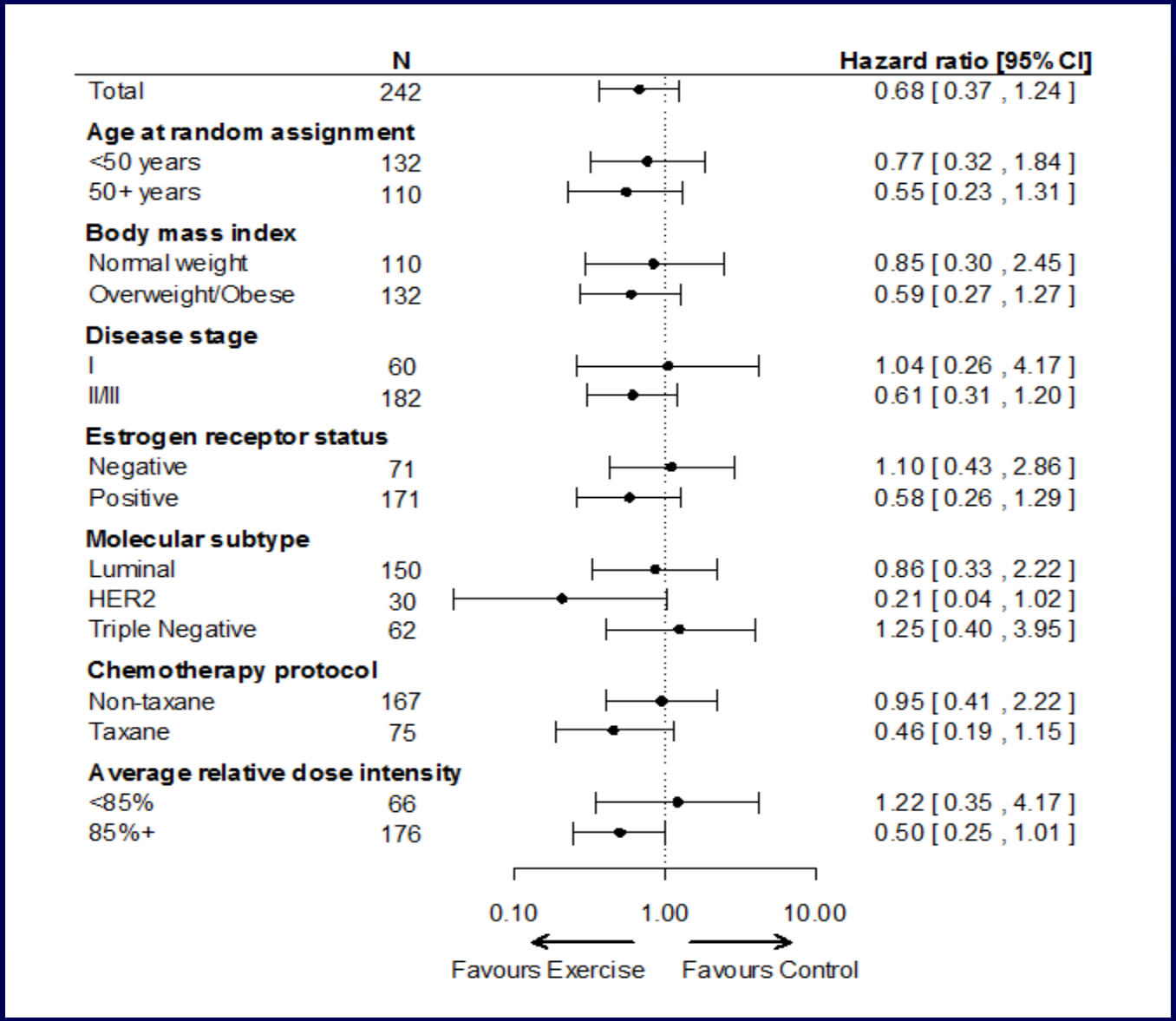
Disease-Free Survival

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



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

Disease-Free Survival by Subgroups



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

Courneya et al. BMC Cancer 2012, 12:525
http://www.biomedcentral.com/1471-2407/12/525

BMC Cancer

STUDY PROTOCOL Open Access

The Alberta moving beyond breast cancer (AMBER) cohort study: a prospective study of physical activity and health-related fitness in breast cancer survivors

Kerry S Courneya[1,10*], Jeff K Vallance[2], S Nicole Culos-Reed[3], Margaret L McNeely[4], Gordon J Bell[1], John R Mackey[5], Yutaka Yasui[6], Yan Yuan[6], Charles E Matthews[7], David CW Lau[8], Diane Cook[1] and Christine M Friedenreich[9]

Courneya et al. BMC Cancer (2016) 16:481
DOI 10.1186/s12885-016-2534-4

BMC Cancer

RESEARCH ARTICLE Open Access

CrossMark

The Alberta Moving Beyond Breast Cancer (AMBER) Cohort Study: Recruitment, Baseline Assessment, and Description of the First 500 Participants

Kerry S. Courneya[1*], Margaret L. McNeely[2], S. Nicole Culos-Reed[3], Jeff K. Vallance[4], Gordon J. Bell[1], John R. Mackey[5], Charles E. Matthews[6], Andria R. Morielli[1], Diane Cook[1], Sarah MacLaughlin[7], Megan S. Farris[7], Stephanie Voaklander[1], Rachel O'Reilly[7] and Christine M. Friedenreich[7]

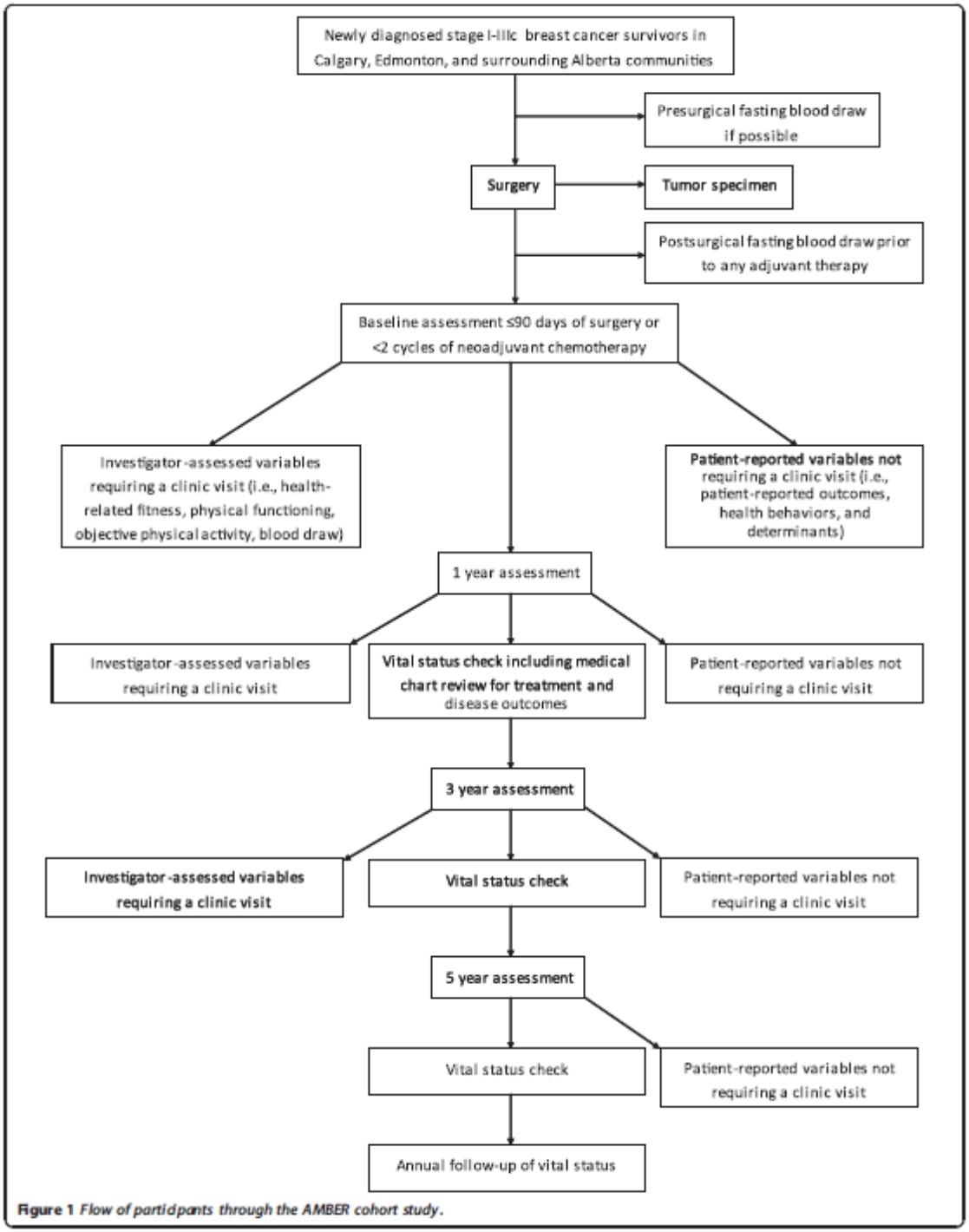
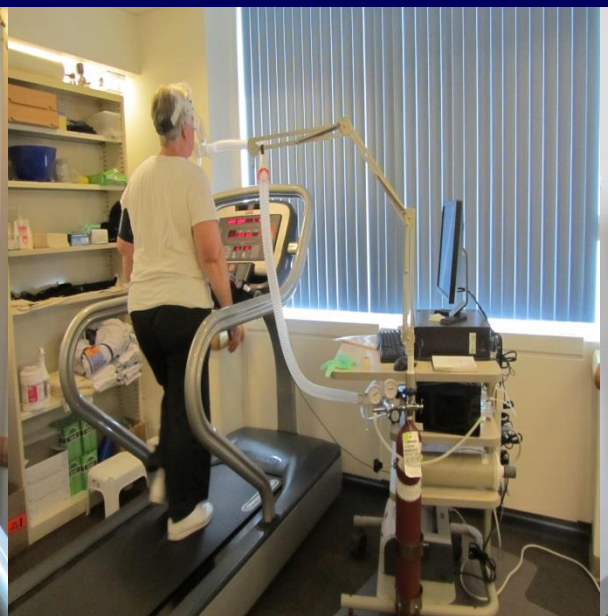


Figure 1 *Flow of participants through the AMBER cohort study.*

AMBER Measures

- comprehensive self-report of PA and SB.
- objective PA and SB (accelerometers/inclinometers).
- maximal cardiorespiratory fitness (gas exchange).
- maximal strength and endurance (8RM, SLT).
- body composition (DXA, anthropometrics).


AMBER Update

- >1,000 breast cancer patients on study.
- 643/696 (92%) assessed at 1 year follow-up.
- 173/199 (87%) assessed at 3 year follow-up.
- 5 year follow-up to start in June, 2017.
- 1,500 accrual completed by December 2018.
- 5 year follow-up completed by December 2023.

CHALLENGE Trial (CO.21)

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†*

Update on the Colon Health and Life-Long Exercise Change Trial: A Phase III Study of the Impact of an Exercise Program on Disease-Free Survival in Colon Cancer Survivors

Kerry S. Courneya · Janette Vardy · Sharlene Gill · Derek Jonker · Patti O'Brien · Christine M. Friedenreich · Haryana Dhillon · Rebecca K. S. Wong · Ralph M. Meyer · Jennifer J. Crawford · Kristin L. Campbell · Harry Prapavessis · Christopher O'Callaghan · Jane Turner · Lissa M. Spencer · Hidde P. van der Ploeg · Dongsheng Tu · Christopher M. Booth

THE CHALLENGE TRIAL

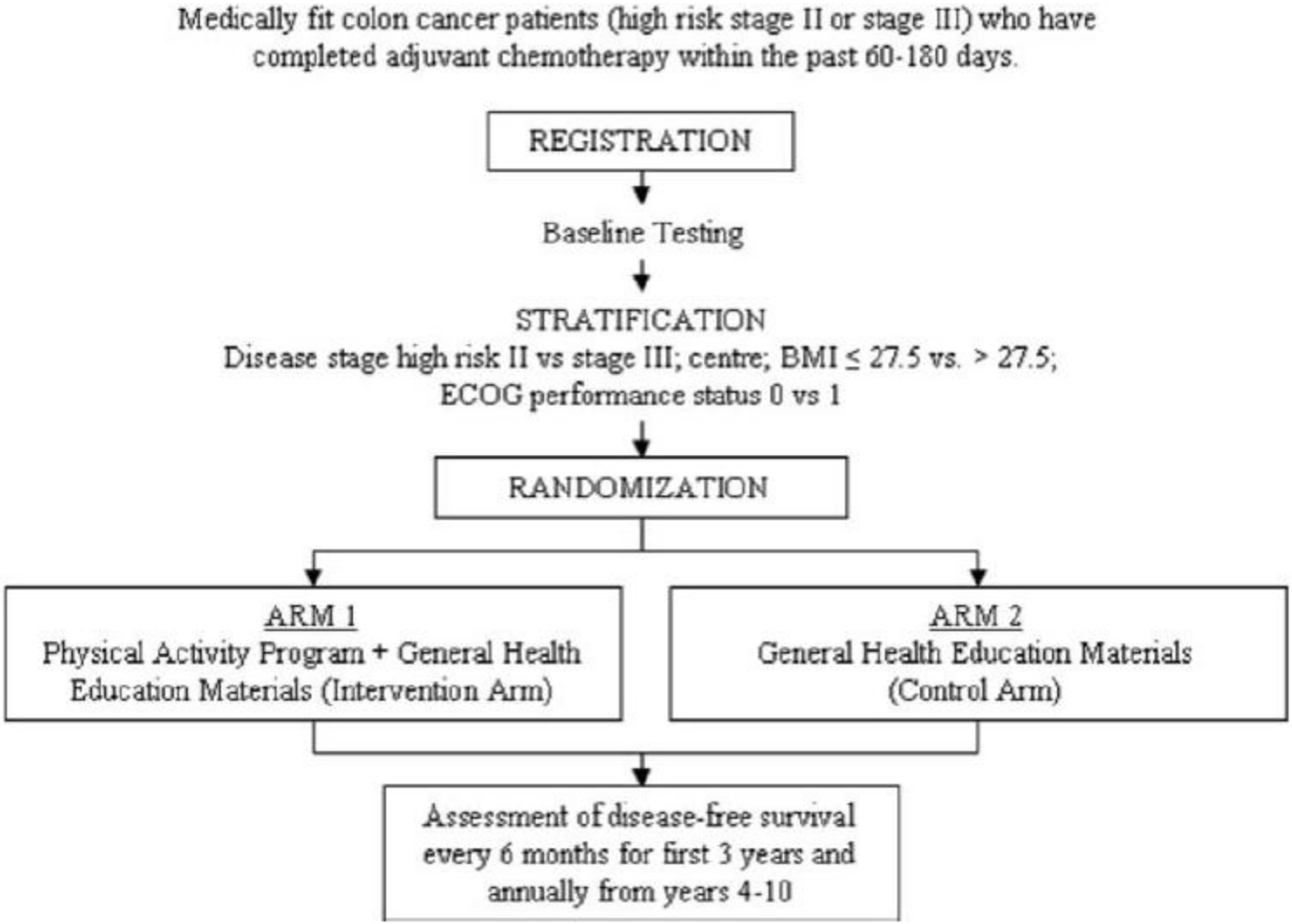


FIGURE 1 Flow of participants through the Colon Health and Life-Long Exercise Change (CHALLENGE) trial.

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Effects of a Structured Exercise Program on Physical Activity and Fitness in Colon Cancer Survivors: One Year Feasibility Results from the CHALLENGE Trial

Kerry S. Courneya[1], Janette L. Vardy[2], Christopher J. O'Callaghan[3], Christine M. Friedenreich[4], Kristin L. Campbell[5], Harry Prapavessis[6], Jennifer J. Crawford[1], Patti O'Brien[3], Haryana M. Dhillon[2], Derek J. Jonker[7], Neil S. Chua[8], Sasha Lupichuk[9], Michael S. Sanatani[10], Sharlene Gill[11], Ralph M. Meyer[12], Stephen Begbie[13], Tony Bonaventura[14], Matthew E. Burge[15], Jane Turner[2], Dongsheng Tu[3], and Christopher M. Booth[16]

(Courneya et al. *Cancer Epi Bio Prev* 2016;25:969-77)

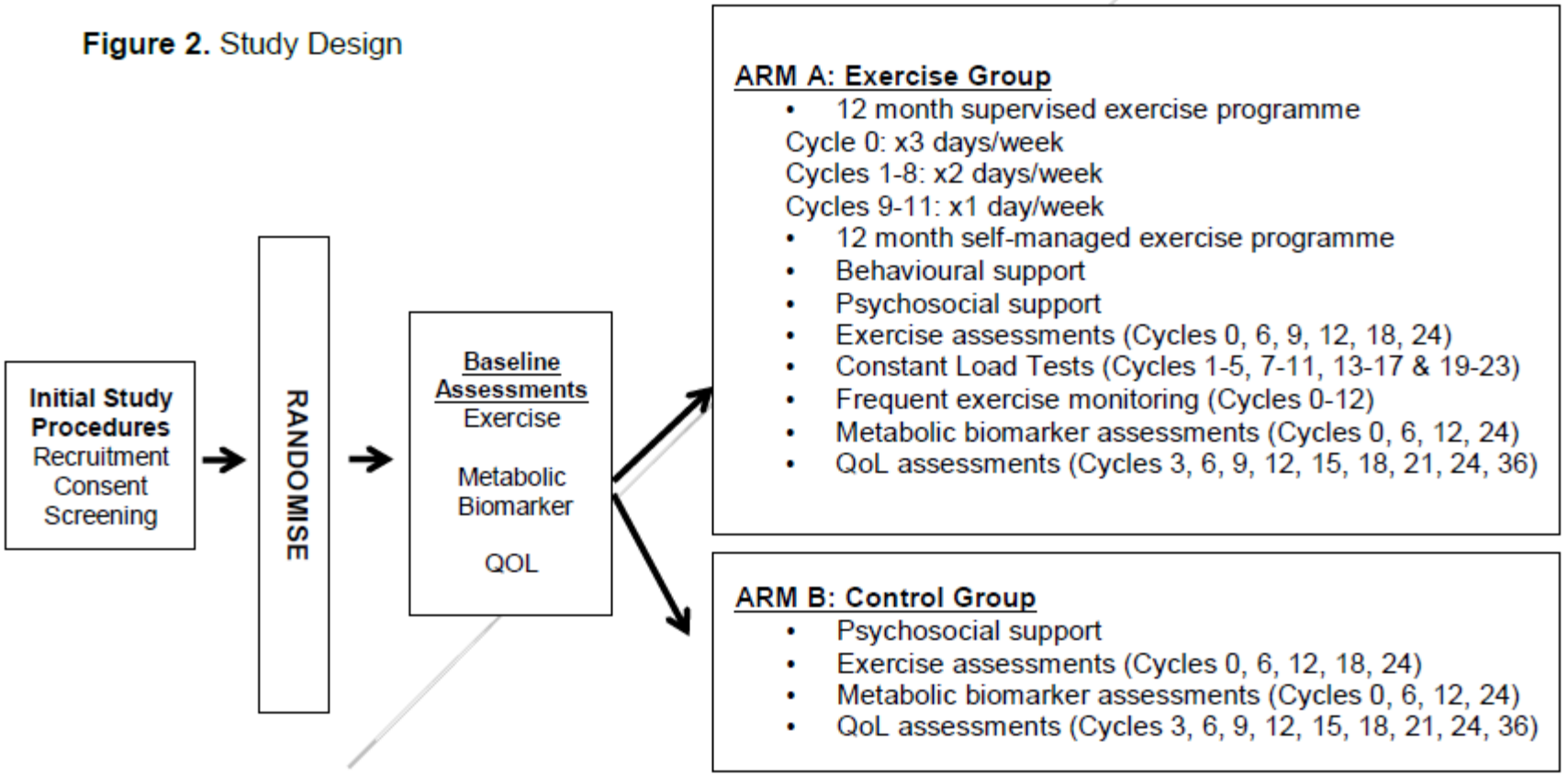
CHALLENGE Trial Update

- ≈20 centers in Canada.
- ≈22 centers in Australia.
- US, Israel, Korea, France
- UK expansion.
- >525 of 962 randomized.
- 3 more years of accrual.
- early efficacy (125 events)

INTERVAL (GAP4) Trial

- phase III RCT of EX and overall survival in 866 prostate cancer patients with M1 CRPC (HR=0.78).
- multinational trial led by Movember Foundation.
- 22 centers in 8 countries have agreed to participate.
- Study Co-Chairs: Fred Saad and Rob Newton.

Figure 2. Study Design



INTERVAL (GAP4) Trial Update

- 1 center has screened 60/randomized 10 in 1 year.
- 2 other centers open for accrual.
- 4 with ethics approval pending site activation.
- 10 pending ethics submission/approval.
- 5 have agreed to participate.

Summary and Conclusions

- self-reported postdiagnosis PA is associated with survival in several cancers (breast, colon, prostate).
- mechanistic data supportive of possible effects.
- precision medicine approach may be informative.
- prospectively designed observational study in breast.
- phase III trials ongoing in colon and prostate.

Acknowledgements

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