

Physical Activity and Cancer Control: From Observational to Experimental Evidence

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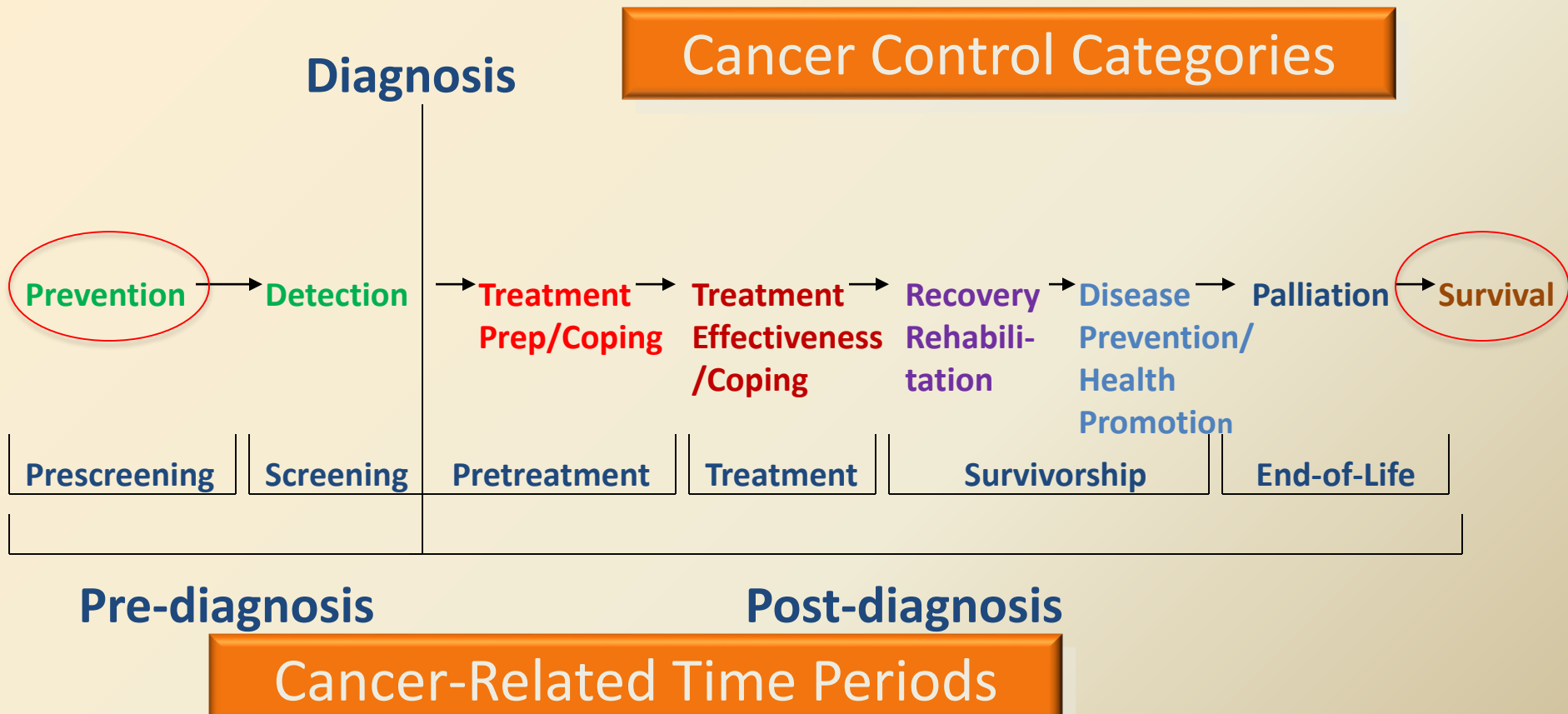
IARC 50th Anniversary Conference

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Physical Activity in Cancer Control Framework

Courneya & Friedenreich (2001, 2007)



Physical Activity and Cancer Risk



Summary of Evidence on Physical Activity and Cancer Risk by Site

Cancer Site	Number of Studies	Studies found reduced risk	Consistency of evidence	Magnitude of risk reduction	Dose-response effect
Breast	111	80	Yes	20-25%	53 of 88
Colon	100	79	Yes	25-30%	43 of 56
Endometrial	32	27	Yes	25-30%	14 of 23
Prostate	60	26	No	<10%	18 of 42
Lung	31	22	Some	20-25%	8 of 11
Pancreas	28	19	Some	10-30%	5 of 17
Ovarian	27	12	No	10-15%	10 of 15

Pooled Data on Leisure-Time Physical Activity and Risk of 26 Types of Cancer

- **Data**: NCI's Cohort Consortium that included 12 prospective US and European cohort studies with 5-12 studies per cancer site
- **Sample**: 1.44 million men (43%) and women (57%), age 19-98 y
- **Exposure**: Self-reported, moderate-vigorous leisure PA
- **Analysis**: Compared HRs for 90th vs. 10th percentiles of activity using random effects meta-analysis
- **Results**: 13 sites have lower risks with higher activity levels; adjusting for BMI slightly attenuated associations except for endometrial cancer and smoking modified effect for lung cancer only

Multivariable HRs for Higher vs Lower Level of Leisure-Time PA by Cancer Type				
Cancer	No. Studies	No. Cases	HR (95% CI)	P-value Trend
Esophageal adenocarcinoma	5	899	0.58 (0.37-0.89)	0.01
Gallbladder	6	382	0.72 (0.51-1.01)	0.06
Liver	10	1384	0.73 (0.55-0.98)	0.04
Lung	12	19113	0.74 (0.71-0.77)	<0.001
Kidney	11	4548	0.77 (0.70-0.85)	<0.001
Small intestine	7	503	0.78 (0.60-1.00)	0.05
Gastric cardia	6	790	0.78 (0.64-0.95)	0.02
Endometrial	9	5346	0.79 (0.68-0.92)	0.003
Esophageal squamous	6	442	0.80 (0.71-1.06)	0.12
Myeloid leukemia	10	1692	0.80 (0.70-0.92)	0.002
Myeloma	9	2161	0.83 (0.72-0.95)	0.008
Colon	12	14160	0.84 (0.77-0.91)	<0.001
Head and neck	11	3985	0.85 (0.78-0.93)	<0.001
Rectum	12	5531	0.87 (0.80-0.95)	0.001
Bladder	12	9073	0.87 (0.82-0.92)	<0.001
Breast	10	35178	0.90 (0.87-0.93)	<0.001

Multivariable HRs for Higher vs Lower Level of Leisure-Time PA by Cancer Type

Cancer	No. Studies	No. Cases	HR (95% CI)	P-value Trend
Non-Hodgkin Lymphoma	11	6953	0.91 (0.83-1.00)	0.01
Thyroid	11	1829	0.92 (0.81-1.00)	0.06
Gastric non-cardia	7	1428	0.93 (0.73-1.19)	0.04
Soft tissue	10	851	0.94 (0.67-1.31)	<0.001
Pancreas	10	4186	0.95 (0.83-1.08)	<0.001
Lymphocytic leukemia	10	2160	0.98 (0.87-1.11)	0.05
Ovary	9	2880	1.01 (0.91-1.13)	0.02
Brain	10	2110	1.06 (0.93-1.20)	0.003
Prostate	7	46890	1.05 (1.03-1.08)	0.12
Malignant melanoma	12	12438	1.27 (1.16-1.40)	0.002
All cancers combined	12	1.44 m	0.93 (0.90-0.95)	NA

Effect of Body Mass Index on Associations with Leisure Time Physical Activity

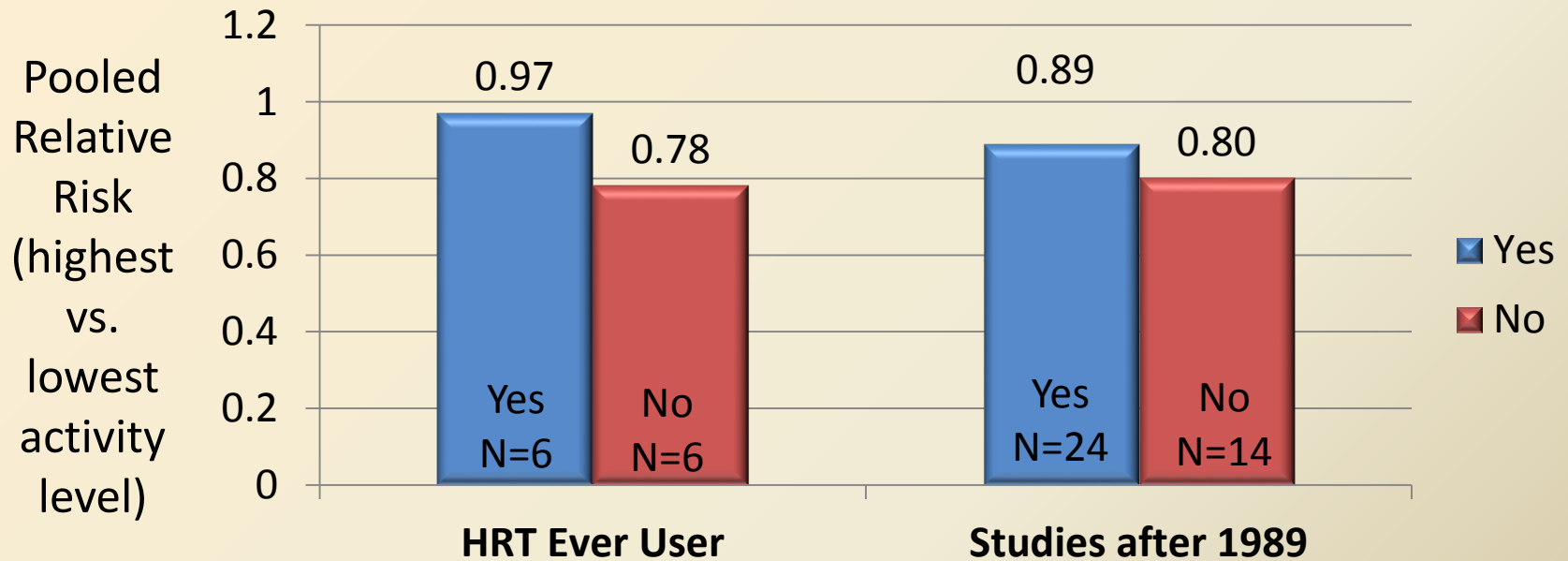
Cancer	Body Mass Index		Difference in HR (%)
	No adjustment	BMI Adjusted	
Liver	0.73 (0.55-0.99)	0.81 (0.61-1.09)	11.0
Kidney	0.77 (0.70-0.85)	0.84 (0.77-0.91)	9.1
Gastric Cardia	0.78 (0.64-0.95)	0.85 (0.69-1.04)	9.0
Endometrial	0.79 (0.68-0.92)	0.98 (0.89-1.09)	24.1

Cancer	Body Mass Index		P-value for Effect Modification
	<25	≥25	
Lung	0.67 (0.62, 0.73)	0.79 (0.74, 0.83)	0.002
Endometrial	1.01 (0.87, 1.16)	0.80 (0.69, 0.93)	<0.001
Small intestine	1.11 (0.68, 1.80)	0.67 (0.47, 0.94)	0.03
Gastric cardia	1.19 (0.79, 1.79)	0.69 (0.54, 0.88)	0.02

Meta-Analyses of Physical Activity and Breast Cancer



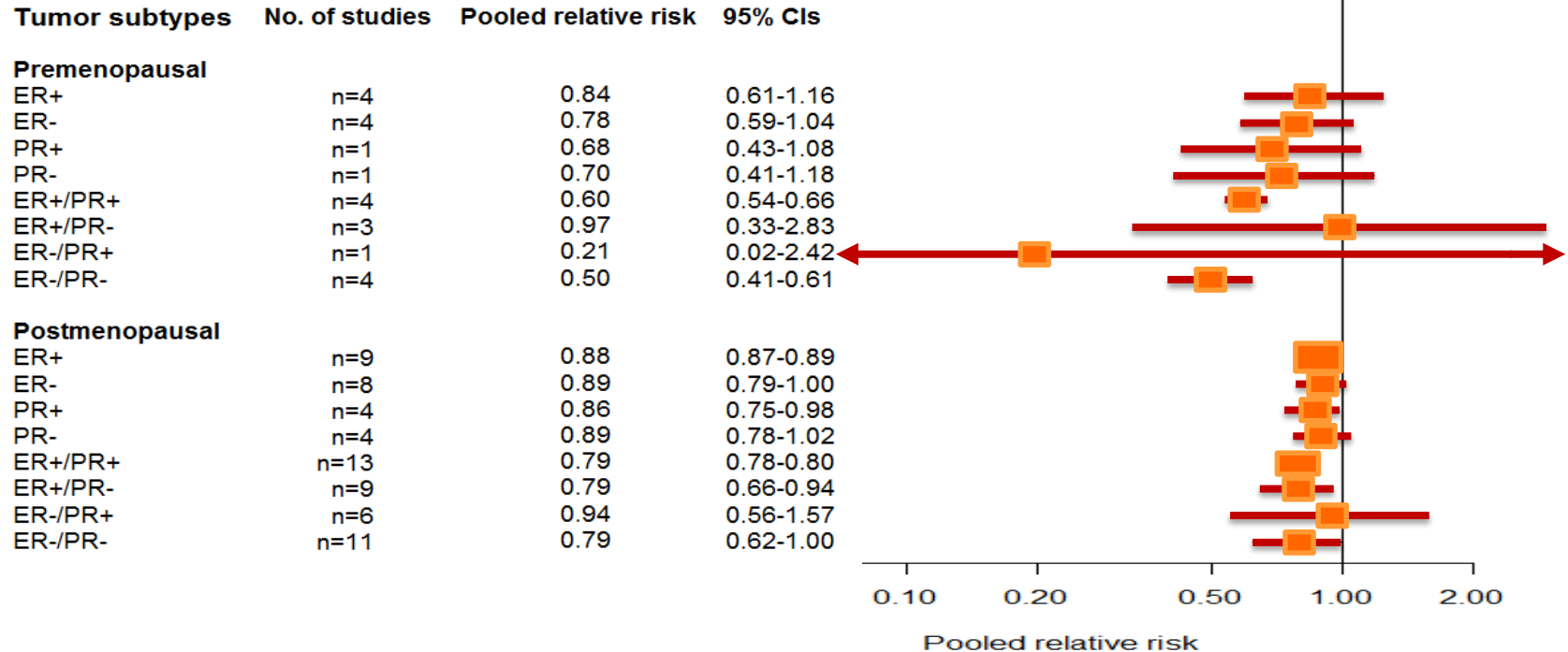
Meta-Analysis of Physical Activity and Breast Cancer: by Hormone Therapy Use



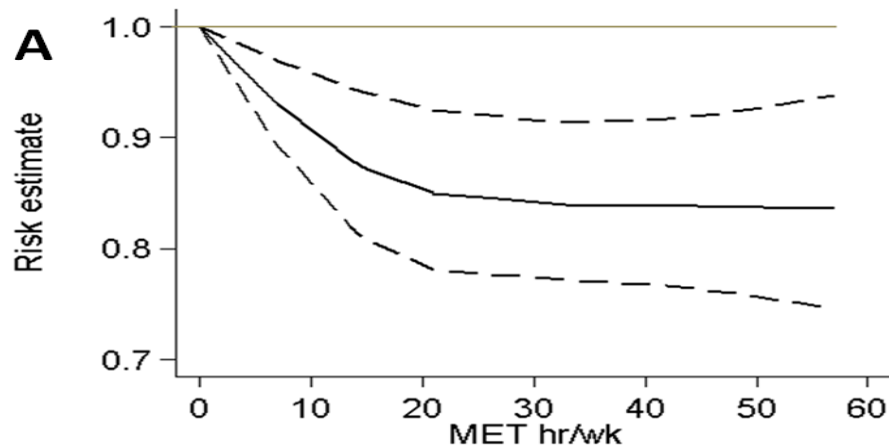
Included 38 prospective studies

Pizot et al. *Eur J Cancer* 2016; 52:138-54

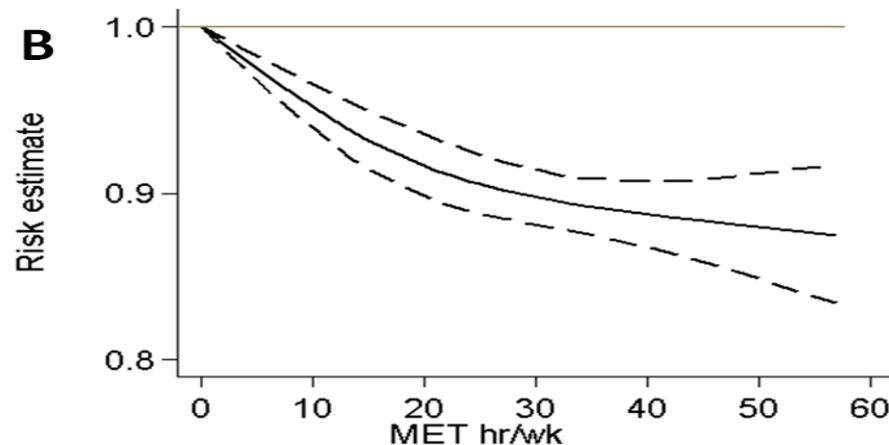
Meta-Analysis of Moderate-Vigorous Recreational Activity and Breast Cancer Risk: by Tumor Subtype



Meta-analysis: Moderate-Vigorous Recreational Activity and Breast Cancer Risk

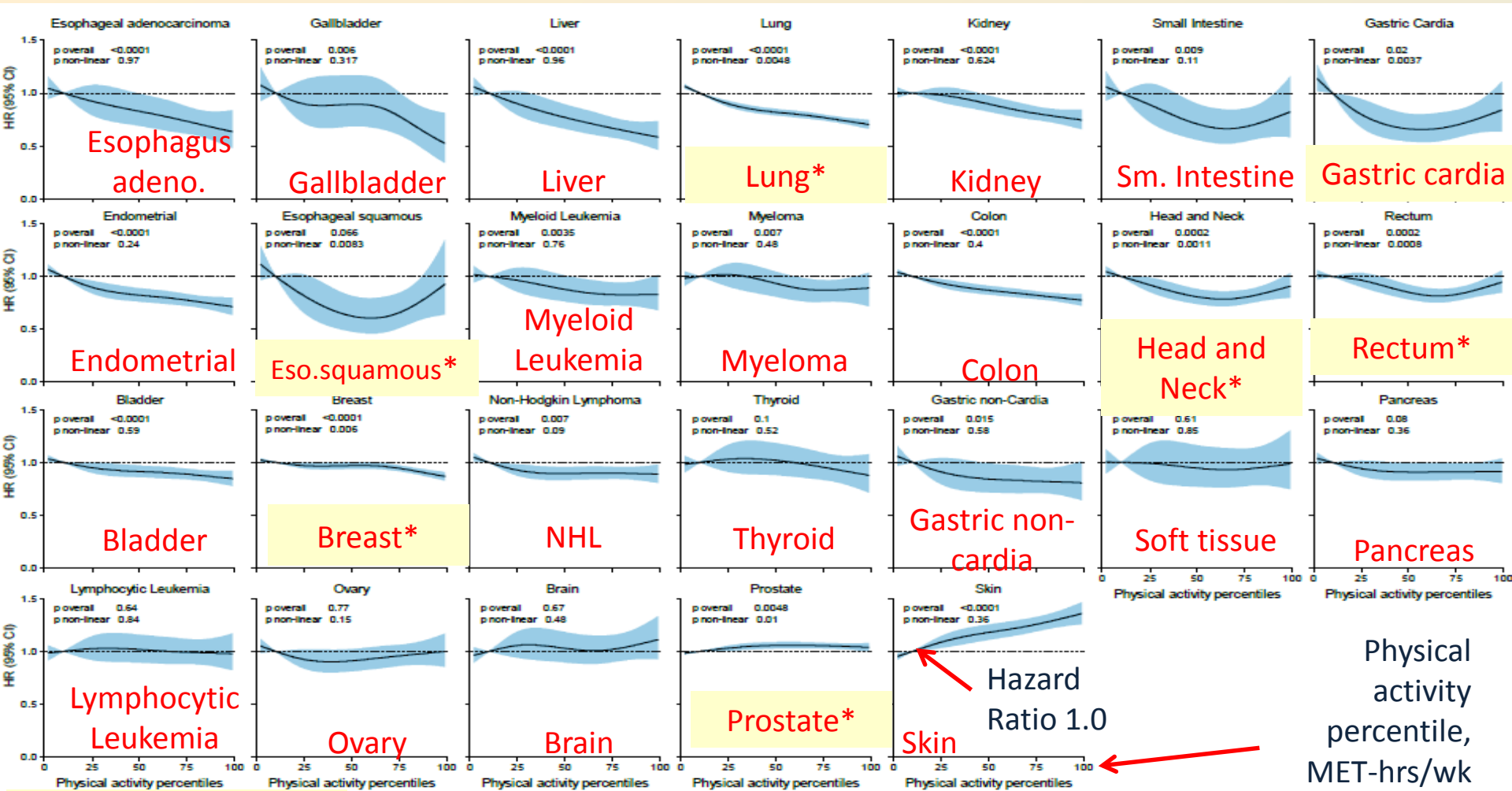


Premenopausal breast
cancer (n=10 studies)



Postmenopausal breast
cancer (n=13 studies)

Change in slope after ~25 MET-hours/week (equals 250 mins/week of 6 METs)



Physical activity percentile, MET-hrs/wk

Hazard Ratio 1.0

* P non-linear <0.05



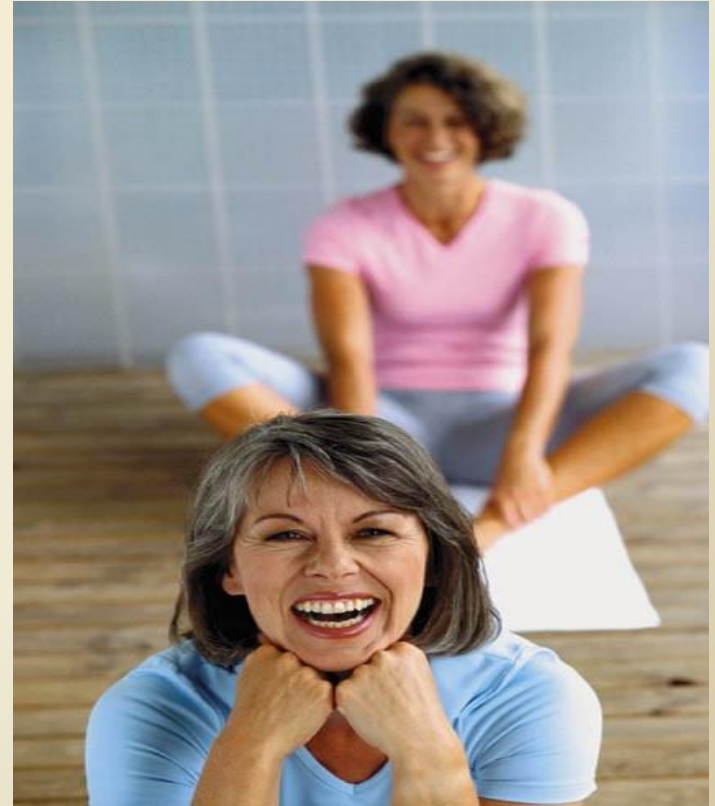
Sedentary Behaviour and Cancer Risk

Summary of Evidence on Sedentary Behaviour and Cancer Risk by Site

Cancer Site	No. of Studies	Studies found increased risk	Consistency of evidence	Magnitude of risk increase	Dose-response effect
Breast	10	3	No	-20% to 41%	1/7
Colorectal	5	2	No	-28% to 56%	3/4
Endometrial	6	6	Yes	15% to 66%	2/4
Ovarian	5	3	Some	6% to 98%	3/4
Lung	3	2	Some	-2% to 36%	0/2
Prostate	2	0	No	-3% to -2%	0/1
Esophageal	2	1	No	-28% to 13%	0/1
Testicular	2	2	Yes	30% to 71%	1/2
Non-Hodgkin Lymphoma	2	1	No	7% to 26%	1/1

Limitations of Observational Studies

- Causality is uncertain e.g., selection bias, confounding
- Difficult to separate effects of:
 - Body fatness from PA
 - PA versus SB
- Lack of objective measures of PA
- Questions remain regarding:
 - Mechanisms
 - Parameters of activity (i.e. duration, intensity, frequency)
 - Type of activity





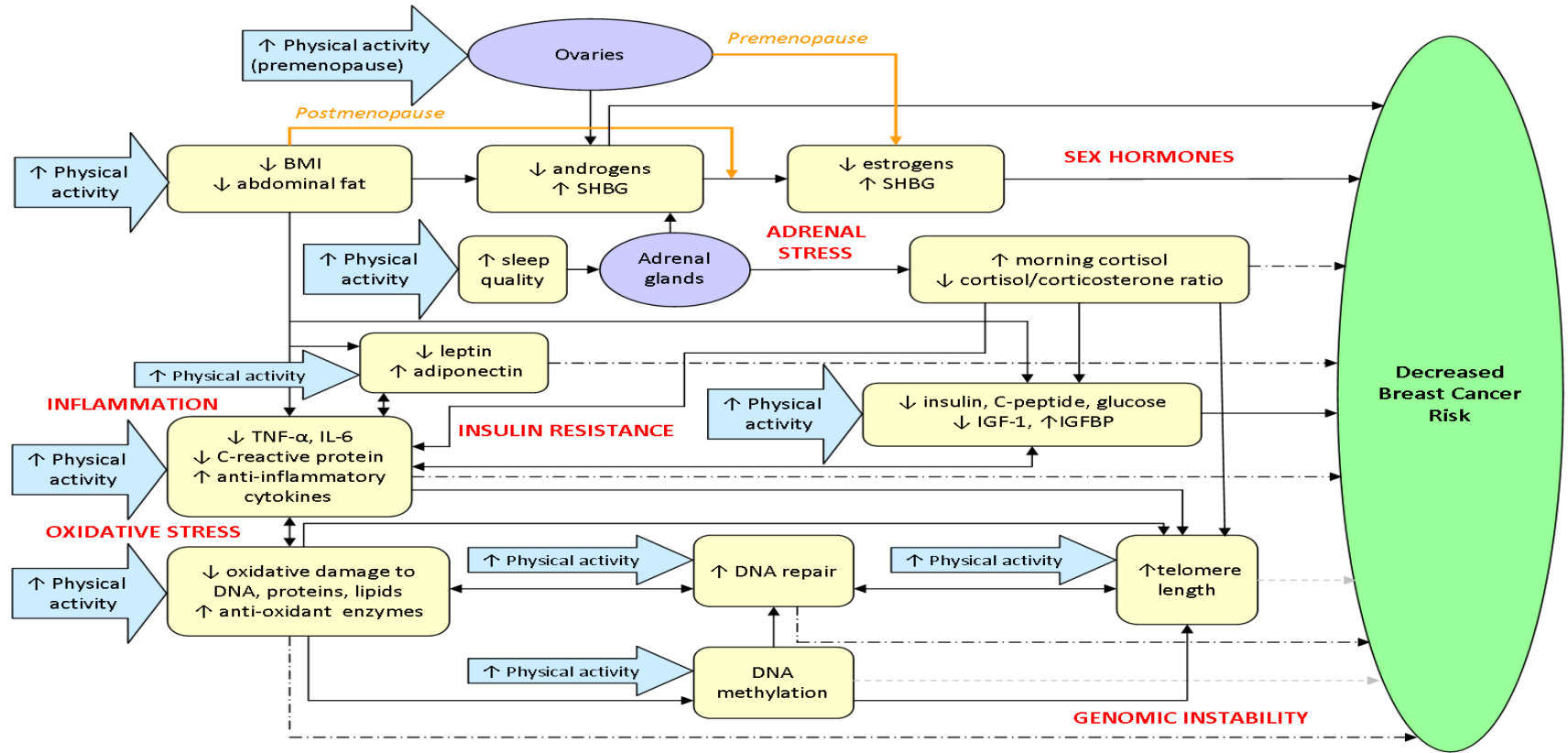
Randomized Trials of Exercise for Breast Cancer Prevention

ALPHA Trial: Design

- **Study design:** Two-armed, two-centered RCT
- **Intervention:** Year-long, 5 days/week, 45 mins/session (3 supervised, 2 unsupervised), aerobic exercise only, no change in diet, 3 mo ramp-up and 9 months maintenance
- **Eligibility criteria:** Postmenopausal, 50-74 yrs, no previous cancer, healthy, BMI=22-40, no HRT use, non-smoker, non-excessive alcohol, inactive
- **Control:** No change in exercise or diet
- **Sample size:** 320
- **Main outcomes:** Sex hormones, adiposity, insulin resistance, inflammation, mammographic density



Hypothesized Biologic Mechanisms Relating Physical Activity to Breast Cancer Risk



Large Randomized Exercise Trials for Postmenopausal Breast Cancer Prevention: Sex Hormones

Trial, duration	Publication	Sample Size	Randomization Group	Free Estradiol % Change	Estrone % Change
PATH 12 months	McTiernan, 2004; <i>Cancer Res</i>	N=87 N=86	Exercise No Exercise	-6.1%	-1.8%
SHAPE 12 months	Monninkhof 2009; <i>J Clin Oncol</i>	N=96 N=93	Exercise No Exercise	-7.3%	-9.7%
ALPHA 12 months	Friedenreich, 2010; <i>J Clin Oncol</i>	N=160 N=160	Exercise No Exercise	-12.9%	-5.4%
NEW 12 months	Campbell, 2012; <i>J Clin Oncol</i>	N=117 N=118 N=117 N=87	Exercise Reduced-calorie Diet Exercise + Diet No Exercise, No Diet	-4.7% -21.4% -26.0%	-5.5% -9.6% -11.1%
SHAPE-2 16 weeks	van Gemert, 2015; <i>Br Cancer Res</i>	N=97 N=98 N=48	Calorie-restricted Diet Exercise + Diet No Exercise, No Diet	-17.7% -19.1%	-1.26% -6.67%

Breast Cancer and Exercise Trial in Alberta (BETA)



Participants in a Canadian Cancer Society-funded exercise and breast cancer prevention trial

Funded by the Alberta Cancer Foundation and the
Canadian Cancer Society, 2010-14
Friedenreich CM, Courneya KS (co-PIs), Stanczyk FS, Yasui Y,
Duha A, Lau DCW, Millikan RC†



Funded by ACF and CCSRI

BETA Study Design

Recruit 400 postmenopausal healthy women 50-74 years

Randomize

High volume exercise group
(5 days/wk x 60 mins/session @
70-80% HRR) (n=200)

Moderate volume exercise group
(5 days/wk x 30 mins/session
@ 70-80% HRR) (n=200)

Compare high vs. moderate exercise groups after **one year** on **endogenous sex hormones, obesity and inflammatory markers, insulin, glucose** (n=386, 97%)

Follow-up at 24 months: examine exercise maintenance and long term effect on biomarkers (n=340, 85%)

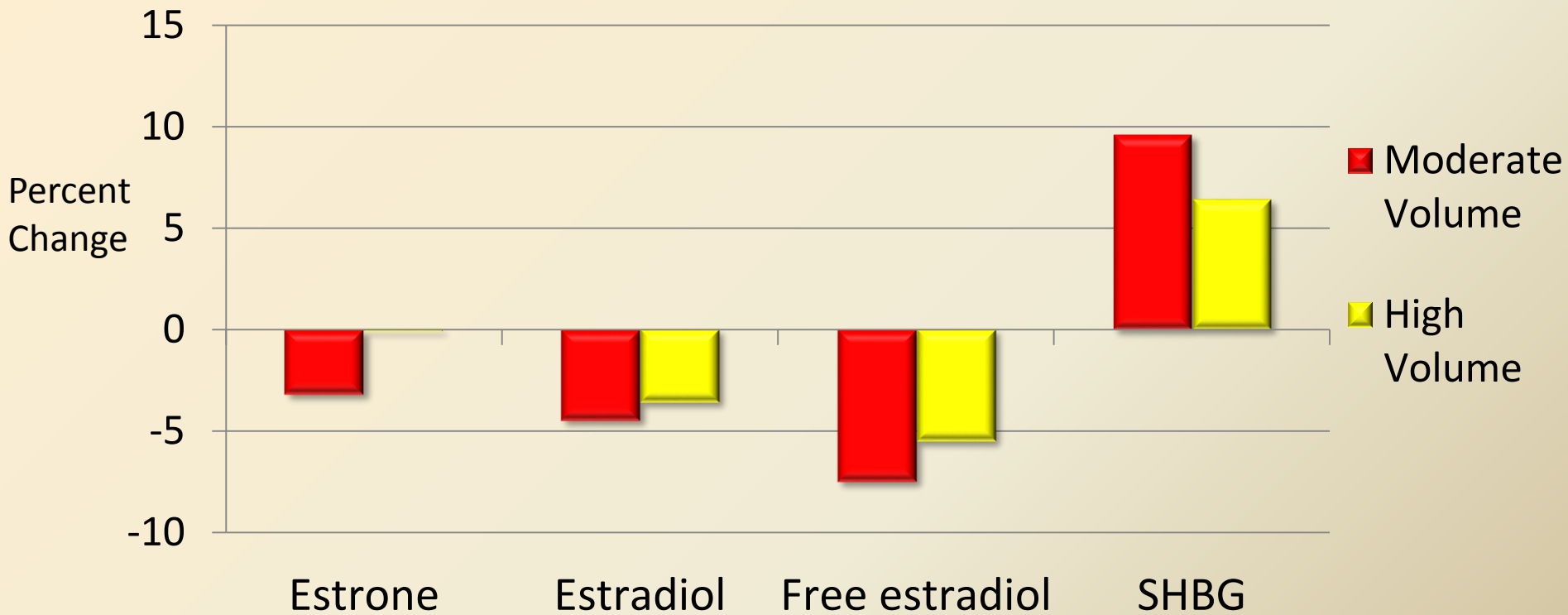


Changes in Adiposity at 12 months by Exercise Group

Change from Baseline (95%CI)	HIGH volume (n=200)	MOD volume (n=200)	Difference (HIGH-MOD)	P-value
Weight (kg)	-2.5 (-3.2, -1.9)	-1.8 (-2.5, 1.1)	-0.7 (-1.6, 0.2)	0.11
Body Mass Index (kg/m ²)	-1.1 (-1.3, -0.8)	-0.7 (-1.0, -0.4)	-0.4 (-0.7, -0.02)	0.04
Percent body fat	-2.2 (-2.7, -1.7)	-1.2 (-1.7, -0.7)	-1.0 (-1.6, -0.4)	0.002
Total fat mass (kg)	-2.4 (-3.0, -1.9)	-1.5 (-2.0, -0.9)	-1.0 (-1.7, -0.2)	0.01
Abdominal fat area (cm ²)	-47.8 (-56, -39)	-36 (-44, -27)	-12 (-24, -0.7)	0.04
Intra-abdominal fat area (cm ²)	-13.4 (-16.7, -10.2)	-11.9 (-15.2, -8.6)	-1.5 (-5.85, 2.85)	0.50

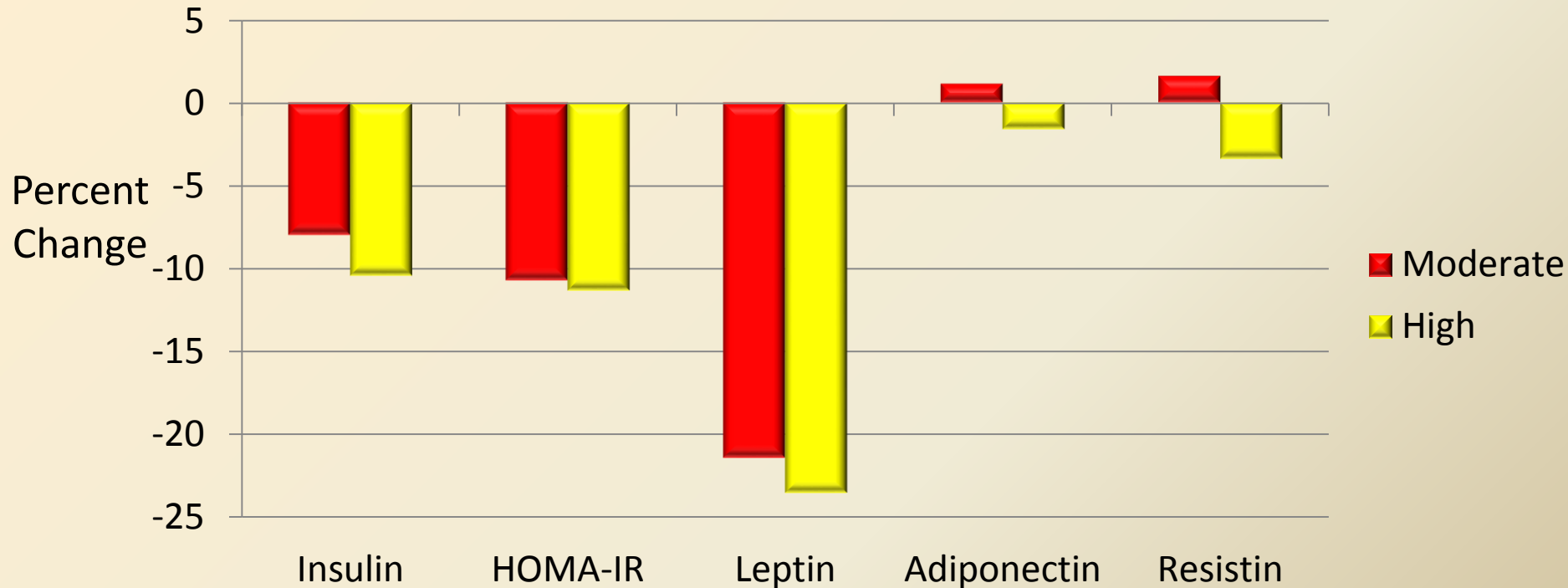


Changes in Sex Hormones at 12 Months by Exercise Group





Changes in Insulin Resistance Indicators at 12 Months by Exercise Group





Changes in Inflammatory Markers at 12 months by Exercise Group





Summary

- Higher duration was more effective for decreasing *total body fat* and *overall abdominal fat*
- No significant dose effects on intra-abdominal fat, estrogens, insulin resistance, or inflammatory markers
- Some dose effects among the per protocol analysis



BETA Participant Marlene Nelson



Physical Activity and Cancer Survival

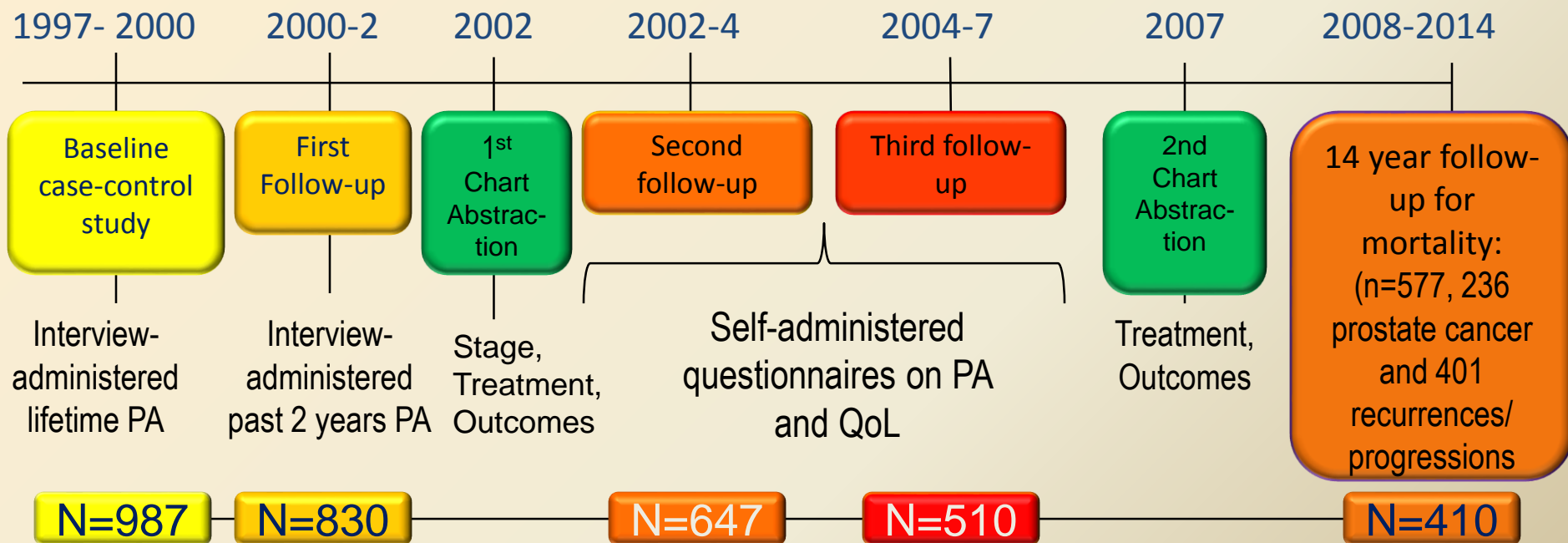
AMBER Study Participant Louise Jefferies

Physical Activity (Pre- and Post-Diagnosis) and Mortality after Cancer

Cancer Site	Number of observational studies	Crude average risk reduction, cancer-specific mortality	Crude average risk reduction, all-cause mortality	Dose-response effect
Breast	26 (+1 RCT)	25%	33%	Some
Colon	15	32%	35%	Some
Prostate	6	8%	48%	NA
Endometrial	2	Null	20%	NA
Ovarian	3	10% *	10%	NA
Lung	1	35%	NA	NA
Glioma	1	NR	55%	NA
Any cancer	3	23%	40%	NA

* Risk increases and decreases of 10% have been reported.

Alberta Cohort Study of Physical Activity and Prostate Cancer Survival, 1997-2014



Multivariate hazard ratios* for **post-diagnosis** physical activity and survival by outcome and type of activity



* Highest (Q4) vs lowest (Q1) quartile

Friedenreich CM et al. *Eur Urology* 2016 Jan 7

Sedentary Behaviour and Cancer Survival



Summary of Evidence on Sedentary Behaviour and Cancer Survival by Cancer Site

Cancer Site	Number of Studies	Studies found increased risk	Consistency of evidence	Magnitude of risk increase	Dose-response effect
Breast	2	2	Yes	21% to 39%	0/1
Colorectal	3	3	Yes	18% to 113%	2/2
Prostate	1	0	NA	-44%	0/1



Alberta Moving Beyond Breast Cancer (AMBER) Cohort Study

Courneya KS, Friedenreich CM (co-PIs), Vallance J, Culos-Reed N, McNeely M, Bell G, Mackey JR, Yasui Y, Lau DCW, Yan Y.

Program Grant Funded by CIHR, 2011-16

Study Design

Study Time Line and Design

2012-2017

Enroll 1500 incident Stage I-IIIc breast cancer cases

Measure physical activity, health-related fitness, determinants of PA, patient-related outcomes, biomarkers, lymphedema

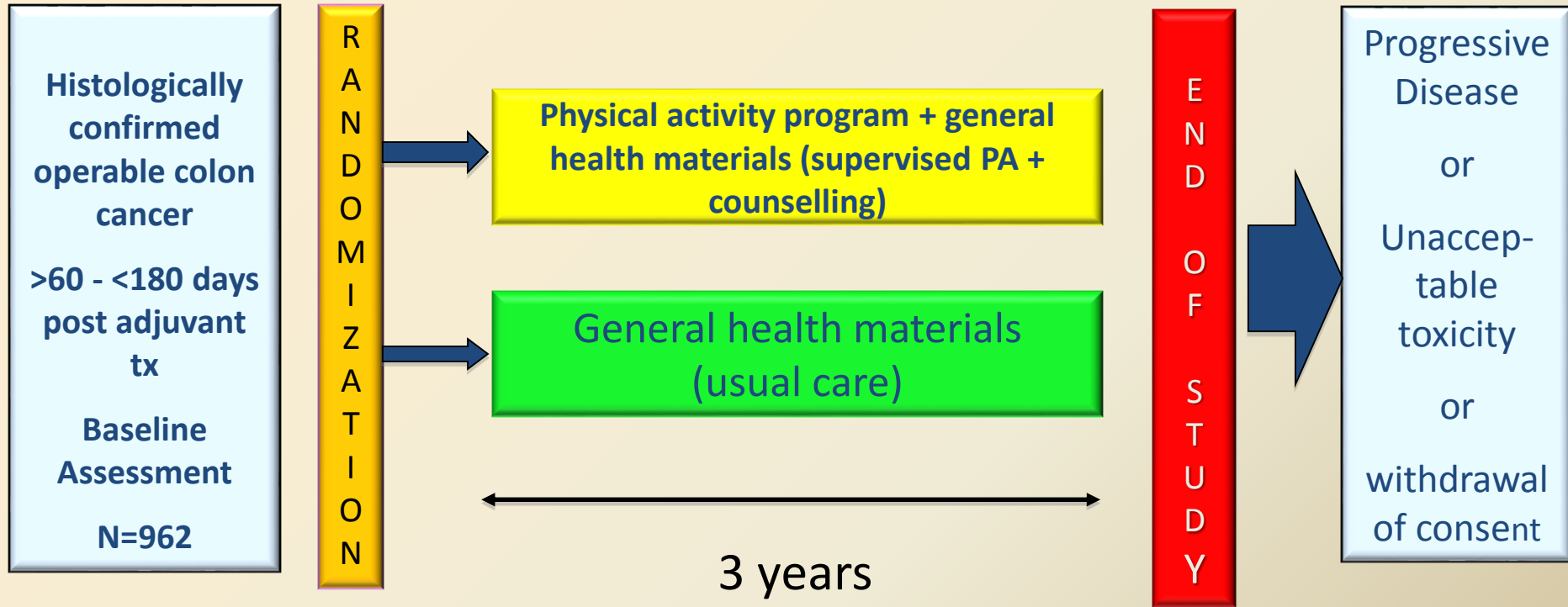
Repeat baseline measurements at 1, 3 and 5 years post-diagnosis

Follow-up for mortality outcomes (disease-specific and all cause)

2017-2022

How can physical activity and health related fitness be used to inform clinical recommendations for improving patient-related outcomes and survival in breast cancer survivors?

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



Primary: disease-free survival

Secondary: PROs, functional capacity, etc.

Courneya et al. *Curr Oncol*, 2008;15:262-70

Courneya et al. *Cancer Epidemiol Biomark Prev* (in press)

Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer

Lee W. Jones, Memorial Sloan Kettering Cancer Center, New York, NY

Discovery

Evaluation
of
Causality

Molecular
epi
studies

Preclinical
Testing

Safety and
Tolerability
Trials

Biomarker-
driven
clinical
trials

Definitive
clinical
trials

Are there molecular subgroups of patients who are responders/non-responders to exercise?

Molecular Epidemiology Studies of Physical Activity and Breast Cancer Survival

Author, Year of Publication	Study	Hypothesized Markers	High category	Low category
Holmes, 2005	Nurses' Health Study	ER+PR+ , ER-PR-	9+ MET-hrs/wk	<9 MET-hrs/wk
Bradshaw, 2014	Long Island Breast Cancer Study Project	ER+PR+ , ER- or PR-	9+ MET-hrs/wk	0 MET-hrs/wk
Chen, 2011	Shanghai Breast Cancer Survival Study	ER+PR+, ER-PR- , ER+PR- or ER-PR+	8.3+ MET-hrs/wk	0 MET-hrs/wk
Bao, 2015	Shanghai Breast Cancer Survival Study	ER-PR-HER2-	7.6+ MET-hrs/wk	0 MET-hrs/wk

Red font: decreased relative risk, statistically significant (p-value < 0.05)

Outcomes were Breast cancer mortality or Breast cancer recurrence/mortality

Friedenreich et al., *Clin Cancer Res* (in press)

Future Directions in Physical Activity and Cancer Prevention and Survival Research

Cancer Prevention

- Explore effect modification by other factors
- Understand biologic mechanisms using biomarker RCTs and molecular epidemiology studies
- Include objective measurements of PA and SB

Cancer Survival

- Examine more cancer sites with objective measurements
- Include molecular and tumour sub-types in analysis
- Investigate biologic and molecular mechanisms
- Conduct more definitive RCTs with survival outcomes

Conclusion

- Physical activity is associated with a reduced risk of several cancers, and possibly improves survival after cancer
- More research will delineate the exact **dose, timing, type** of activity that is most effective for cancer control as well as the underlying **mechanisms** and possible **sub-groups** who may benefit more from physical activity



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- ◆ Alberta Innovates Health Solutions
- ◆ Alberta Cancer Foundation



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■ Staff and Trainees:

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