

Physical Activity Influences on Cancer Risk and Survival

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Overview

- Physical activity across the cancer continuum:
 - ◆ Prevention
 - ◆ Treatment
 - ◆ Rehabilitation
 - ◆ Survival
- Review of evidence from:
 - ◆ Observational studies
 - ◆ Randomized controlled exercise intervention trials
- Biologic mechanisms in physical activity and cancer control:
 - ◆ RCT evidence for cancer prevention, rehabilitation and survival
- Future research directions

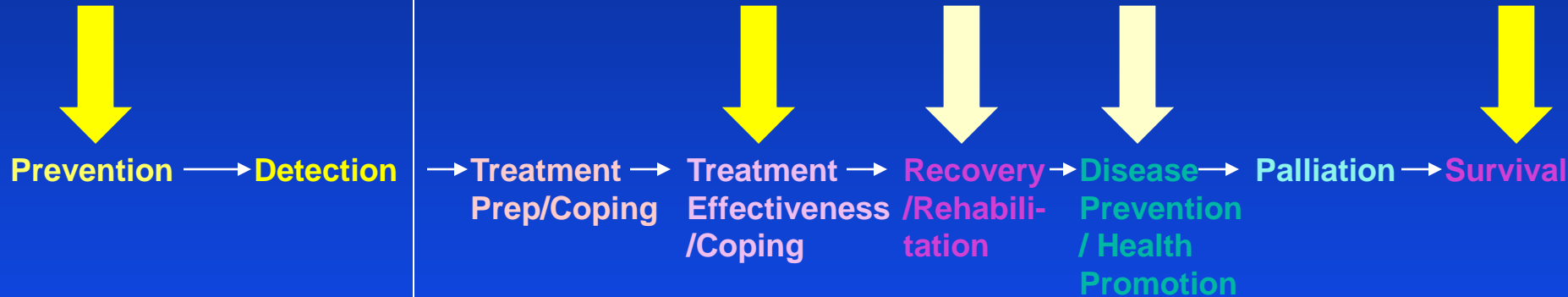


Physical Activity in Cancer Control Framework

Courneya & Friedenreich (2001, 2007)

Diagnosis

Cancer Control Categories



Prescreening

Screening

Pretreatment

Treatment

Survivorship

End-of-Life

Prediagnosis

Postdiagnosis

Cancer-Related Time Periods

Physical Activity and Cancer

Courneya and Friedenreich, editors

Recent Results in Cancer Research
P.M. Schlag · H.-J. Senn *Series Editors*

Kerry S. Courneya
Christine M. Friedenreich
Editors

Physical Activity and Cancer

Indexed in PubMed/Medline

 Springer

■ Topics:

- ◆ Physical Activity and Cancer Prevention
- ◆ Physical Activity and Cancer Survivorship
- ◆ Physical Activity and Cancer Special Topics

Recent Results in Cancer Research,
Springer-Verlag, 2011

Level of Evidence on Physical Activity and Cancer Risk Reduction

Convincing or Probable

Colon

Breast

Endometrial

Weaker evidence

Lung

Prostate

Ovarian

Insufficient or Null

Rectal *

Pancreatic

Gastric

Bladder

Testicular

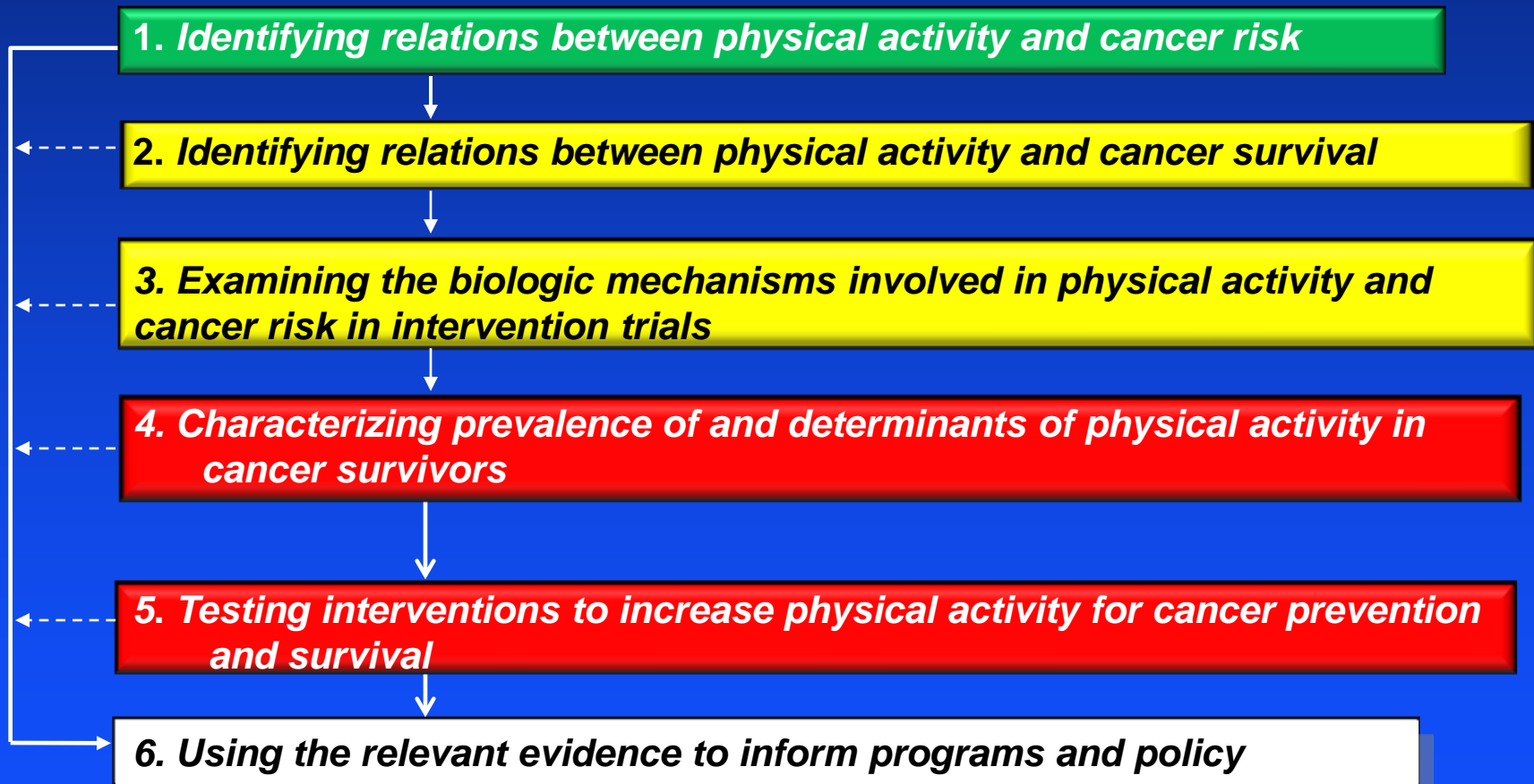
Kidney

Hematologic cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, multiple myeloma)

** No association*

Physical Activity and Cancer Research: State of the Science

 Strong evidence base  Modest evidence base  Limited evidence base



Physical Activity and Breast Cancer Risk

Lynch BM, Neilson HK, Friedenreich CM.
Physical activity and breast cancer prevention.

In Courneya KS and Friedenreich CM (eds). Physical Activity and Cancer. Recent Results in Cancer Research. Heidelberg:Springer-Verlag, 2011.

Summary of Evidence on Physical Activity and Breast Cancer Risk

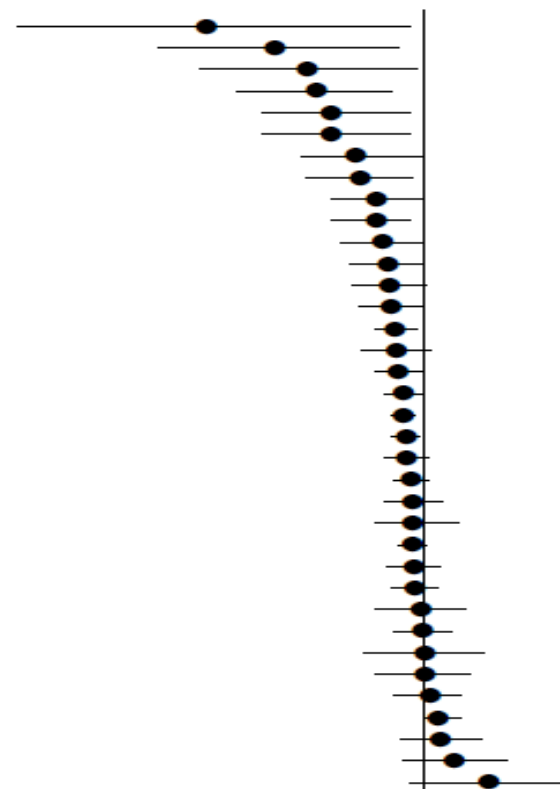
- Consistent evidence (*66 out of 88 observed decreased risk*):
 - ◆ 19 studies show no effect
 - ◆ 66 studies show decreased risk
 - ◆ 3 studies find increased risks
- Fairly strong risk reductions (*25% decrease for highest vs. lowest activity levels, on average*)
 - ◆ 31% average risk reduction in case-control studies
 - ◆ 19% average risk reduction in cohort studies
- Clear dose-response with increasing activity and decreasing risk (*40 of 50 studies*)
- Biologic plausibility exists (*several possible mechanisms*)
- Temporality exists

Lynch et al. in Courneya and Friedenreich, Physical Activity and Cancer. Heidelberg: Springer-Verlag, 2011

Physical Activity and Breast Cancer Risk: Cohort Studies

Prospective

Cerhan et al, 1998
Breslow et al, 2001
Wyrwich et al, 2000
Suzuki et al, 2008
Sesso et al, 1998
Thune et al, 1997
Lee et al, 2001
George et al, 2010
Patel et al, 2003
Fraser et al, 1997
Suzuki et al, 2011
Dirx et al, 2001
Maruti et al, 2008
McTiernan et al, 2003
Dallal et al, 2007
Chang et al, 2006
Rockhill et al, 1999
Phipps et al, 2011
Eliassen et al, 2010
Peters et al, 2009
Leitzmann et al, 2008
Tehard et al, 2006
Howard et al, 2009
Inoue et al, 2008
Bardia et al, 2006
Lahmann et al, 2007
Silvera et al, 2006
Kabat et al, 2010
Pronk et al, 2011
Mertens et al, 2005
Luoto et al, 2000
Colditz et al, 2003
Calle et al, 1998
Schnohr et al, 2005
Margolis et al, 2005
Dorgan et al, 1994



Retrospective

Wyshak et al, 2000
Rintala et al, 2002
Pijpe et al, 2009
Moradi, 2002
Rintala et al, 2003
Paffenbarger, 1987



Statistically significant reduction in 16 of 42 cohort studies (38%)

0.001

0.01

0.125

0.5

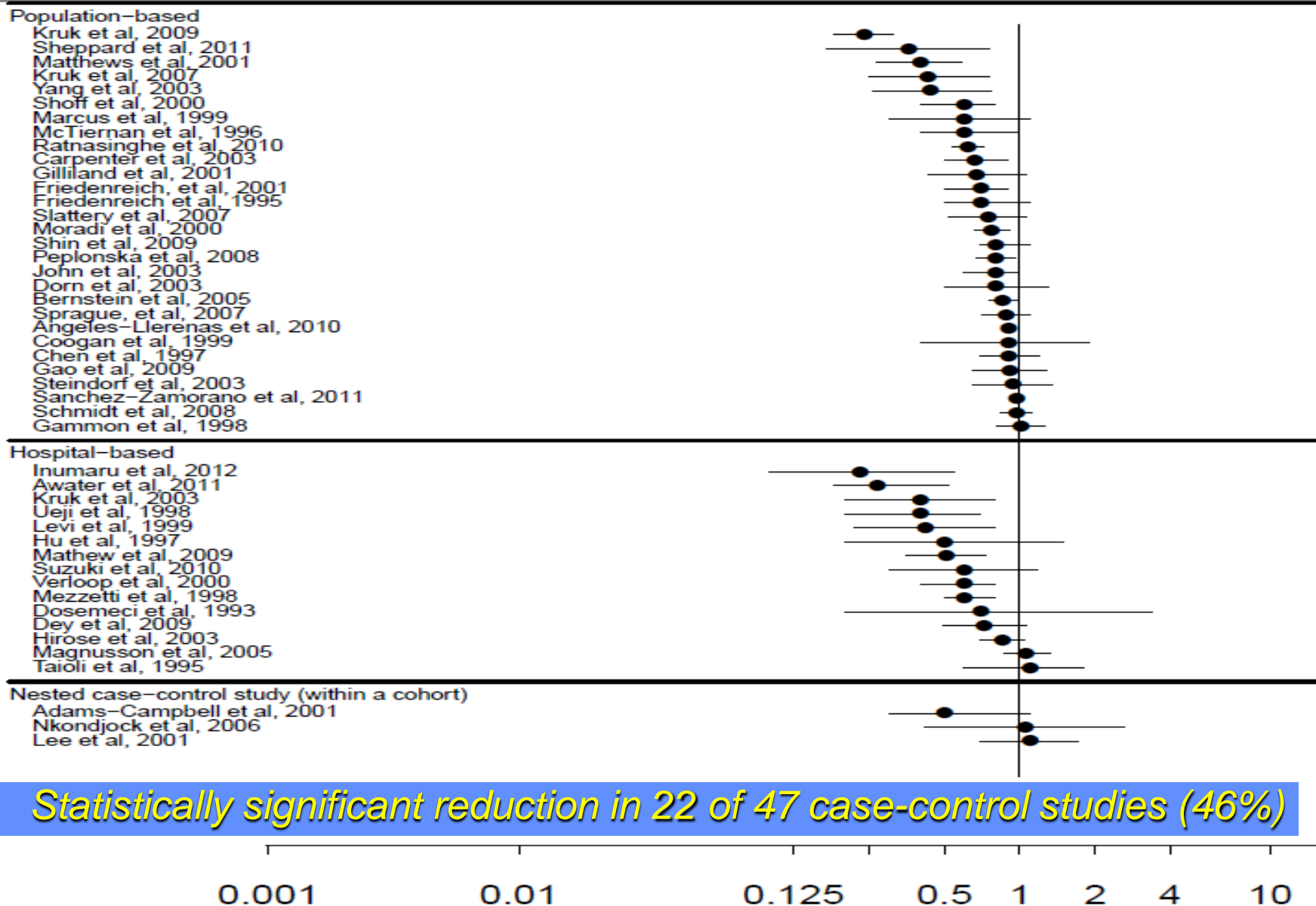
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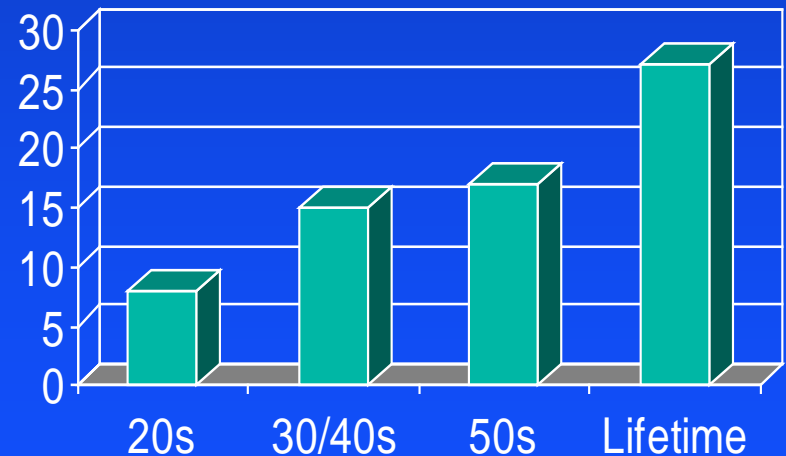
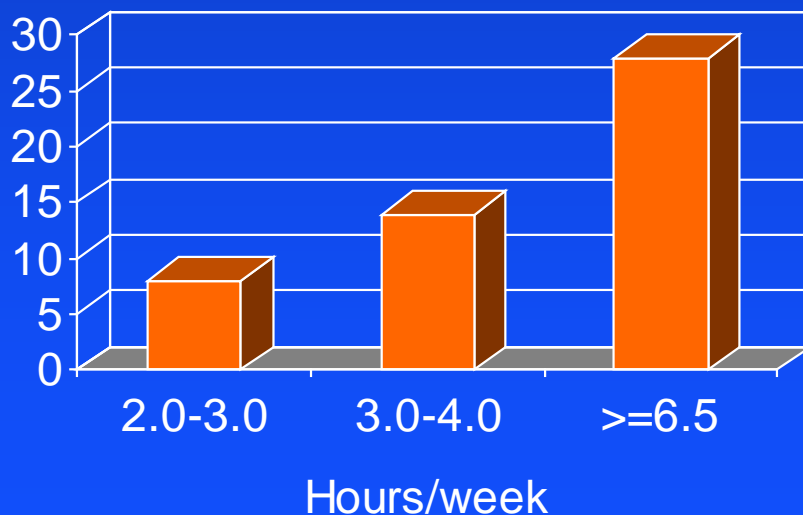
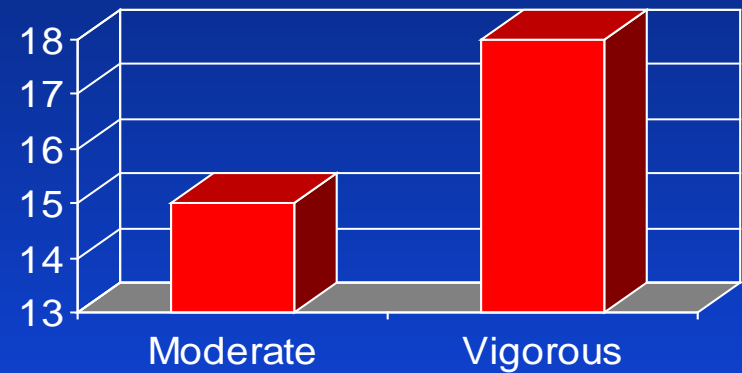
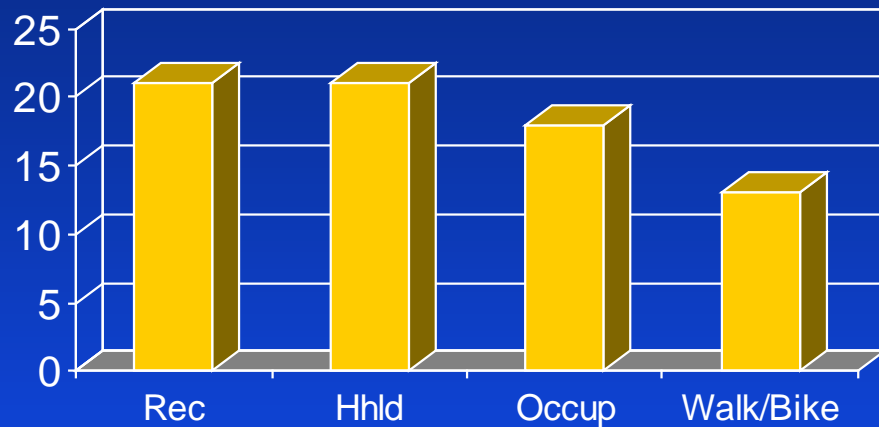
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Physical Activity and Breast Cancer Risk: Case-control Studies

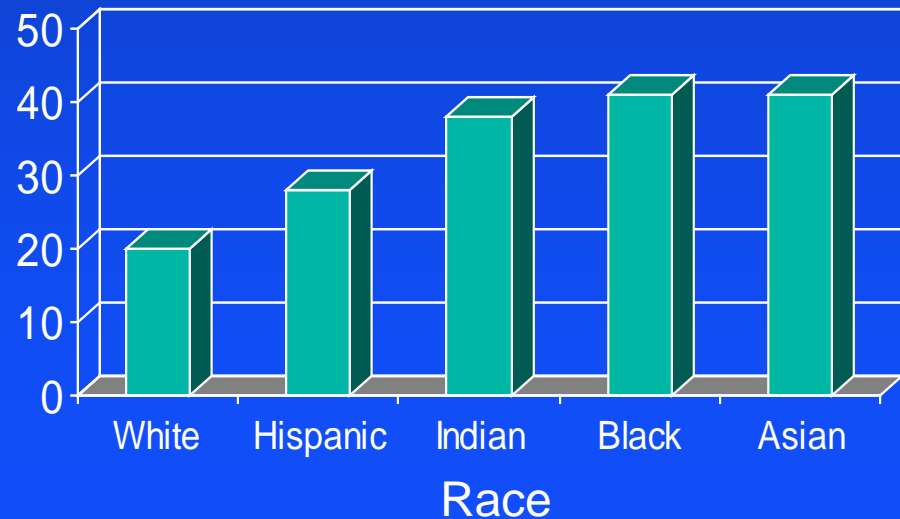
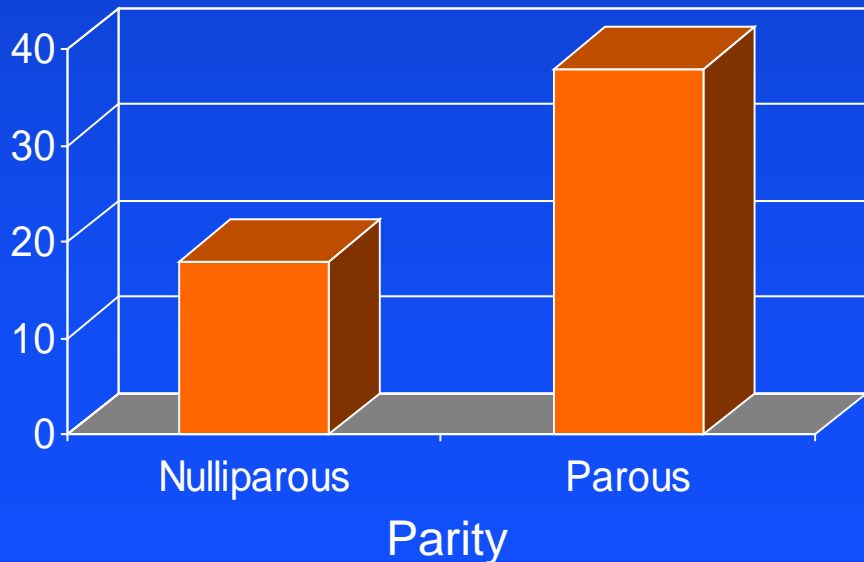
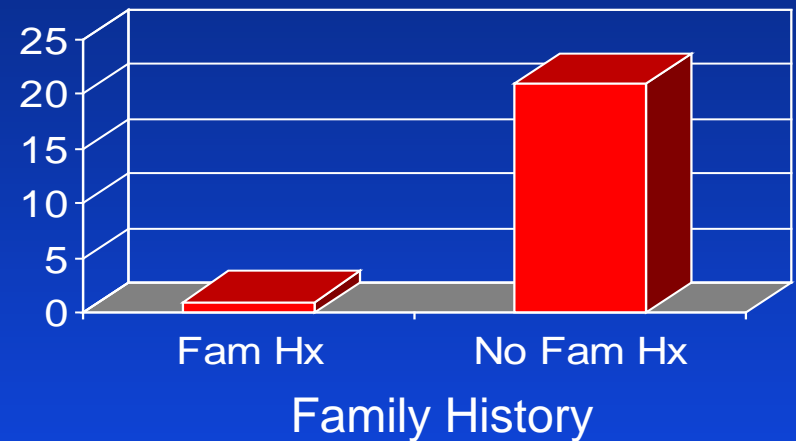
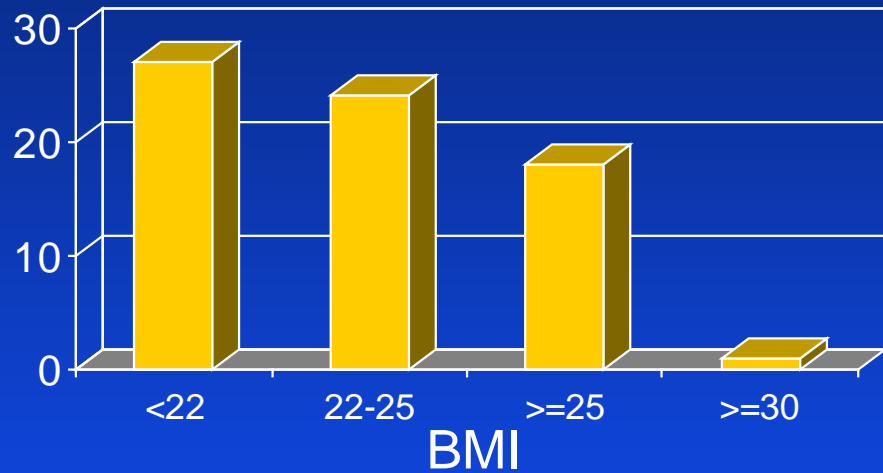


Statistically significant reduction in 22 of 47 case-control studies (46%)

Breast Cancer Risk Reduction by Type, Dose and Timing of Activity



Population Subgroup Effects for Physical Activity and Breast Cancer



Physical Activity and Risk of Colon Cancer

Summary of Evidence on Physical Activity and Colon Cancer Risk

- Consistent evidence (*72 of 86 studies*)
 - ◆ 15 show no effect and no studies find increased risk
- Fairly strong risk reductions (*~30% decreases for highest vs. lowest activity levels*)
 - ◆ 27% average risk reduction in case-control studies
 - ◆ 20% average risk reduction in cohort studies
- Clear dose-response (*41 of 47 studies*)
- Biologic plausibility exists
- Temporality exists

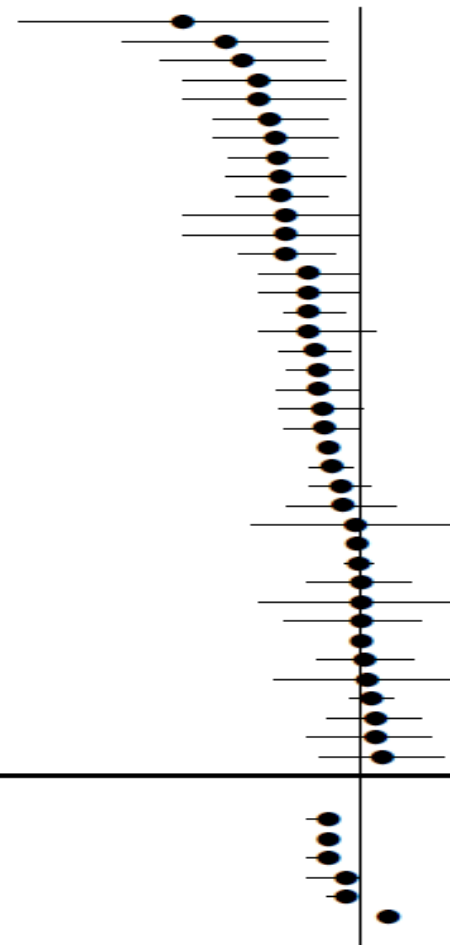
Physical Activity and Colon Cancer Risk: Cohort Studies

Prospective

Gerhardsson et al, 1988
Wu et al, 1987
Colbert et al, 2001
Giovannucci et al, 1995
Martinez et al, 1997
Lund Nilssen et al, 2001
Takahashi et al, 2007 Male
Larson et al, 2006
Lee et al, 2007
Inoue et al, 2008
Ballard-Barbash et al, 1990
Hsing et al, 1998
Chao et al, 2004
Lynge et al, 1988
Severson et al, 1989
Will et al, 1998
Schnohr, 2005
Nilsen et al, 2008
Wei et al, 2004
Mai et al, 2007
Wolin et al, 2007
Friedenreich et al, 2006
Marti et al, 1989
Howard et al, 2008 Male
Howard et al, 2008 Female
Morrison et al, 2012
Wannamethee et al, 2001
Johnsen et al, 2006 Male
Yun et al, 2008
Bostick et al, 1994
Steenland et al, 1995
Thune et al, 1996
Johnsen et al, 2006 Female
Hermann et al, 2009
Takahashi et al, 2007 Female
Wolin et al, 2010
Lee et al, 1994
Lee et al, 1997
Calton et al, 2006

Retrospective

Gerhardsson et al, 1986
Chow et al, 1994
Moradi et al, 2008 Male
Chow et al, 1993
Moradi et al, 2008 Female
Paffenbarger et al, 1987



Statistically significant risk reductions in 16 of 41 studies (39%)

0.001

0.01

0.125

0.5

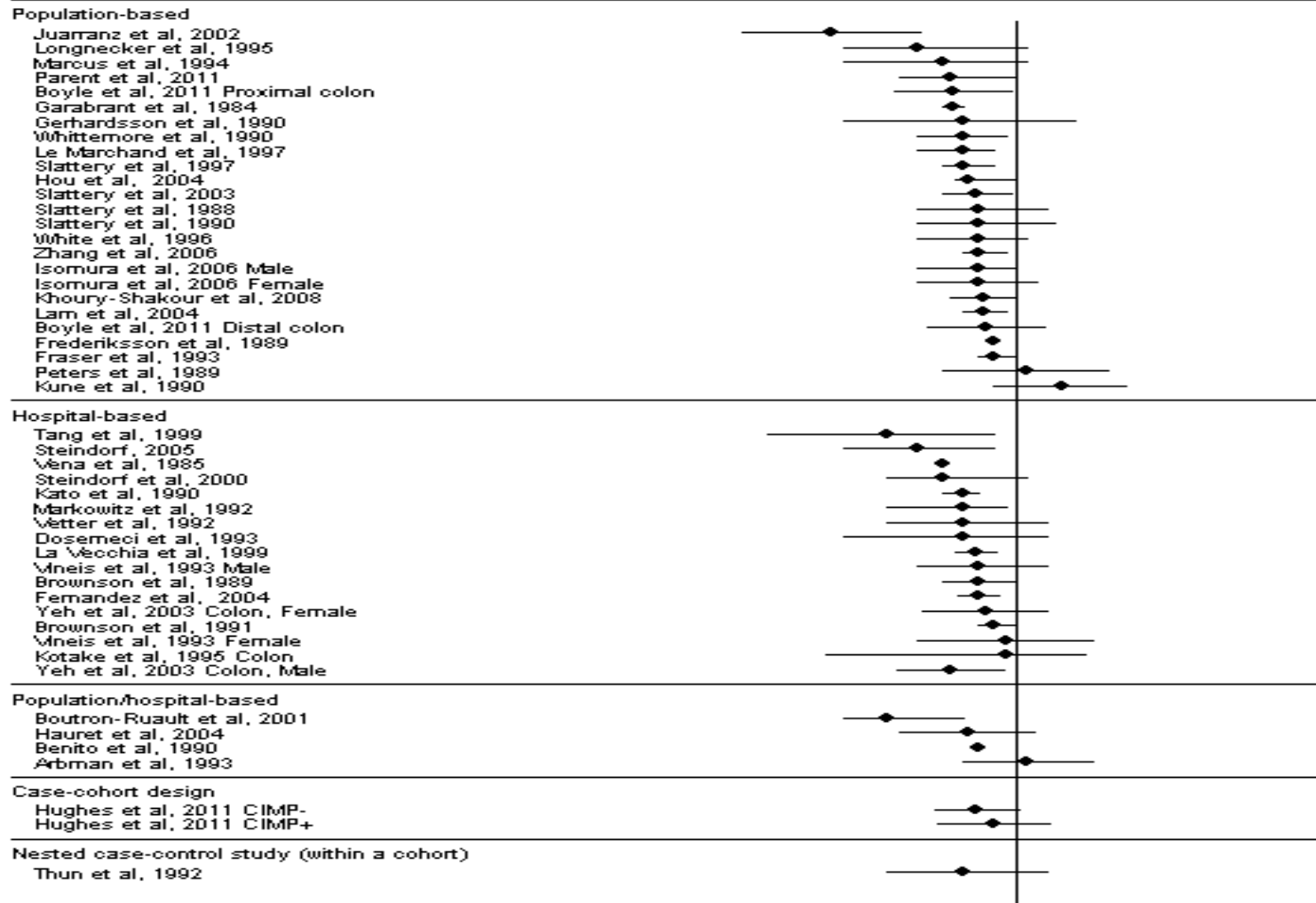
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Physical Activity and Colon Cancer Risk: Case-control Studies



Statistically significant risk reductions in 18 of 44 studies (41%)

Type, Dose and Timing of Activity: Colon Cancer

■ Type of Activity

- ◆ All types may be effective for lowering risk
 - ☞ e.g., occupational activity (22% decrease in risk), recreational (23%)
- ◆ Sedentary behaviour may increase risk

■ Intensity

- ◆ Vigorous or moderate activity decrease risk

■ Timing of activity

- ◆ Inconsistent findings

■ Population Sub-groups

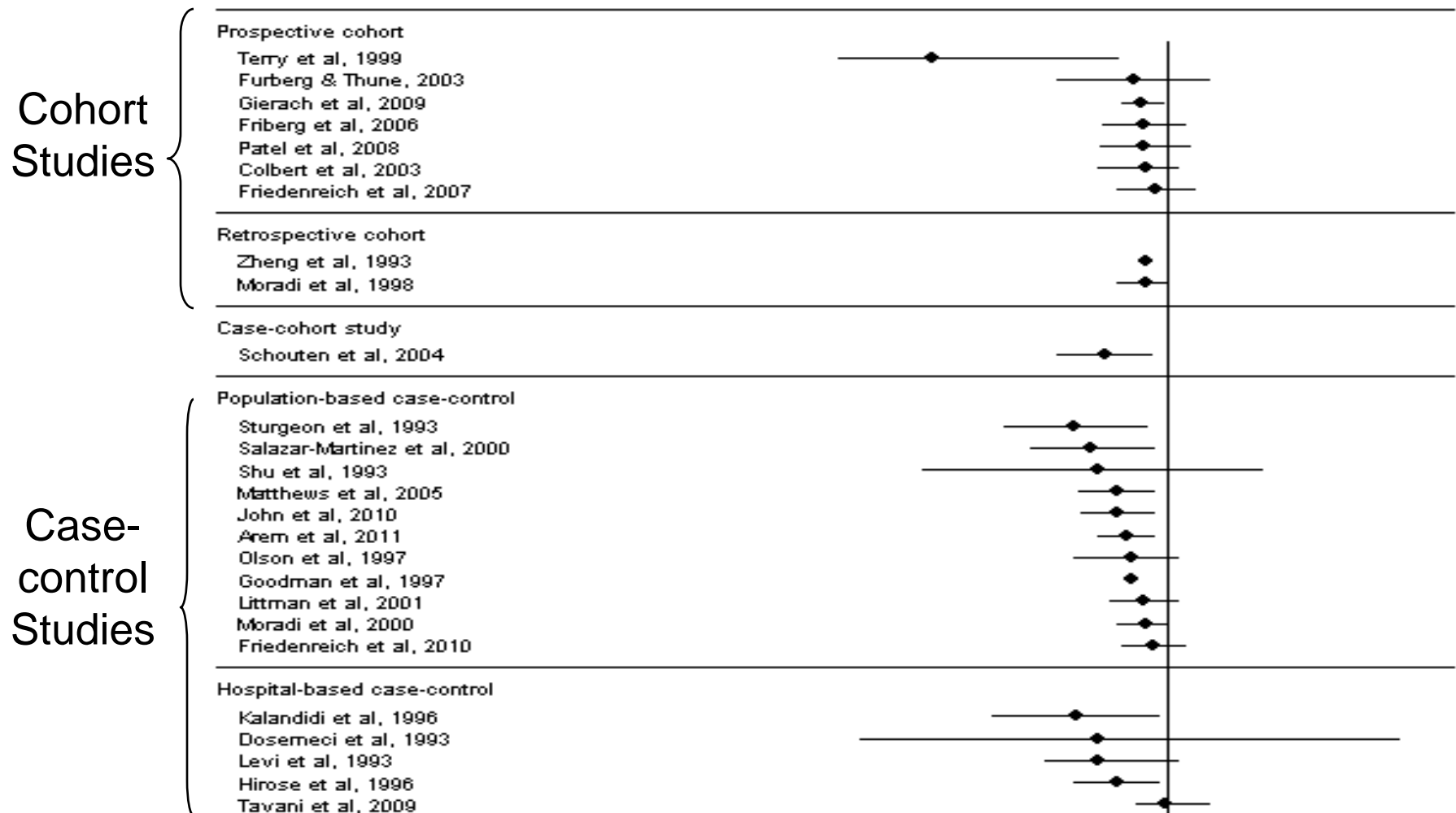
- ◆ Relatively constant effects across BMI categories
- ◆ Association may vary by tumour sub-site
 - ☞ i.e., proximal or distal
- ◆ Benefit for men and women
- ◆ Unclear effects of race/ethnicity, dietary intake, HRT use

Physical Activity and Risk of Gynecologic Cancer

Summary of Evidence on Physical Activity and Endometrial Cancer Risk

- Consistent evidence (*23 of 28 studies*)
 - ◆ Nearly all of studies show risk reductions
- Fairly strong risk reductions (*30-35% decreases for highest vs. lowest activity levels*)
 - ◆ 25% average risk reduction in cohort studies
 - ◆ 37% average risk reduction in case-control studies
- Evidence of dose-response (*12 of 19 studies*)
- Biologic plausibility exists
- Sedentary behaviour emerging as possibly important

Physical Activity and Endometrial Cancer Risk



Statistically significant risk reduction in 14 of 28 studies (50%)

0.001

0.01

0.125

0.5

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Summary of Evidence on Physical Activity and Ovarian Cancer Risk

- Moderately consistent evidence (*12 of 24 studies*)
 - ◆ 12 studies show risk reductions
 - ◆ 3 studies show increased risk (1 is statistically significant)
- Weak risk reductions (*<10% average decreases for highest vs. lowest activity levels*)
 - ◆ Average 10% increased risk in cohort studies
 - ◆ Average 25% decreased risk from case-control studies
- Some evidence of dose-response (*9 of 11 studies*)

Physical Activity and Ovarian Cancer Studies

Cohort
Studies

Prospective

Schnohr et al, 2005
Hannan et al, 2005
Biesma et al, 2006
Patel et al, 2006
Bertone et al, 2001
Weiderpass, 2006
Weiderpass et al, 2012
Leitzmann et al, 2009
Lahmann et al, 2009
Anderson et al, 2004
Chionh et al, 2010

Case-
control
Studies

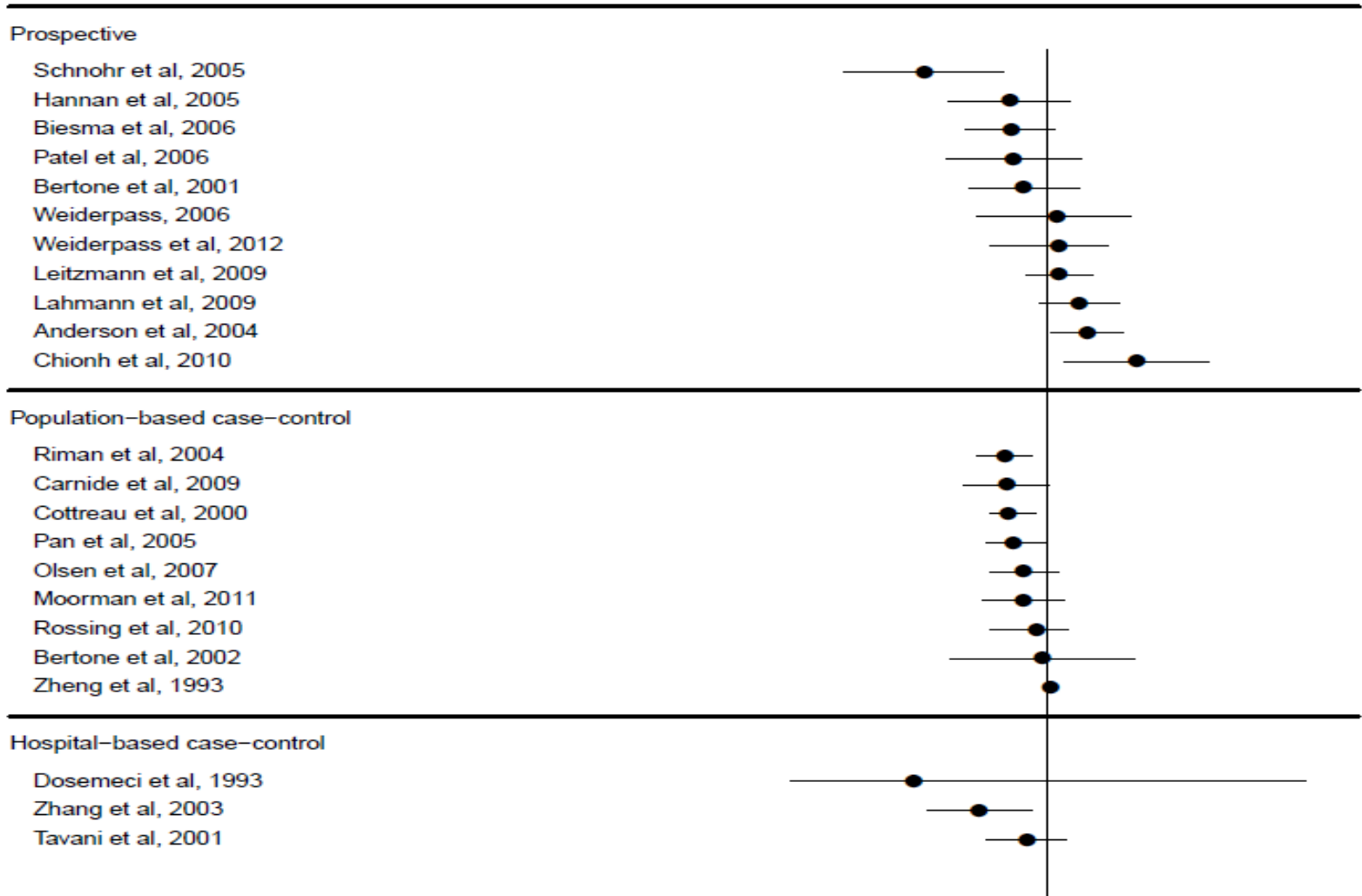
Population-based case-control

Riman et al, 2004
Carnide et al, 2009
Cottreau et al, 2000
Pan et al, 2005
Olsen et al, 2007
Moorman et al, 2011
Rossing et al, 2010
Bertone et al, 2002
Zheng et al, 1993

Hospital-based case-control

Dosemeci et al, 1993
Zhang et al, 2003
Tavani et al, 2001

0.001 0.01 0.125 0.5 1 2 4 10



Physical Activity and Risk of Prostate Cancer

Summary of Evidence on Physical Activity and Prostate Cancer Risk

- Less consistent evidence (*26 of 56 studies*)
 - ◆ 25 studies find no effect
 - ◆ 26 studies find decreased risk
 - ◆ 5 studies find increased risk
- Weak risk reductions (*10% decreases for highest vs. lowest activity levels*)
- Evidence of dose-response (*12 of 18 studies*)
 - ◆ about half of the studies that examined these trends
- Some biologic plausibility exists

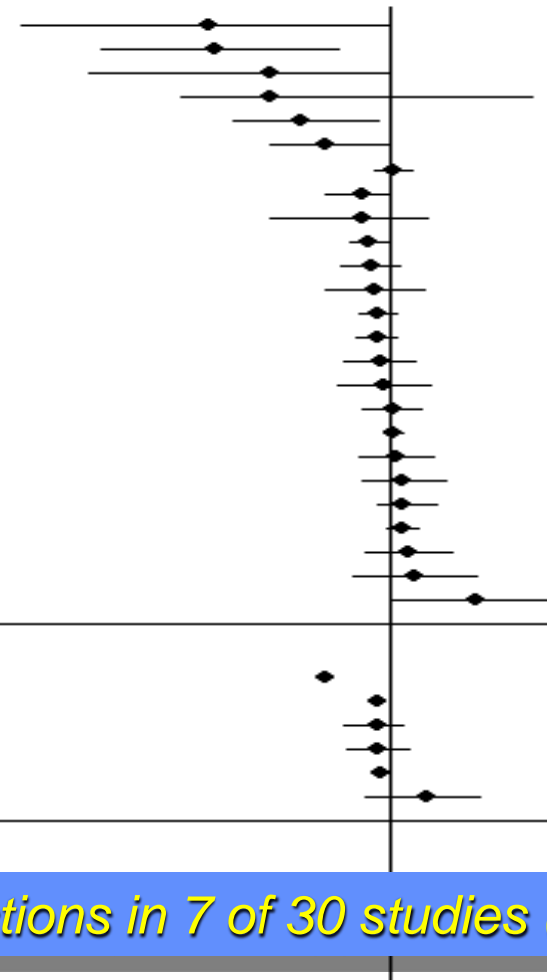
Physical Activity and Prostate Cancer: Cohort Studies

Prospective

Wannamethee et al, 2001
Giovannucci et al, 2005
Oliveria et al, 1996
Hartman et al, 1998
Clarke and Whittemore, 2000
Thune and Lund, 1994
Johnsen et al, 2009
Lund Nilsen et al, 2000
Steenland et al, 1995
Orsini et al, 2009
Nilsen et al, 2006
Moore et al, 2009
Patel et al, 2005
Johnsen et al, 2009
Littman et al, 2006
Schnohr, 2005
Zeegers et al, 2005
Moore et al, 2008
Lee et al, 2001
Severson et al, 1989
Liu et al, 2000
Giovannucci et al, 2007
Inoue et al, 2008
Crespo et al, 2008
Ceran et al, 1997

Retrospective

Paffenbarger et al, 1987
Norman et al, 2002
Hsing et al, 1994
Yun et al, 2008
Vena et al, 1987
Pukkala et al, 2000



Statistically significant risk reductions in 7 of 30 studies (23%)

0.001

0.01

0.125

0.5

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Physical Activity and Prostate Cancer: Case-control Studies

Population-based

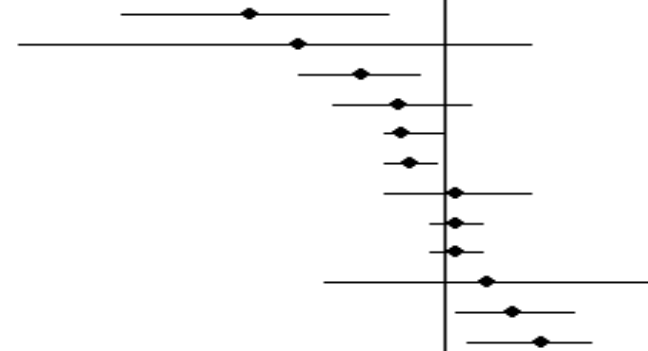
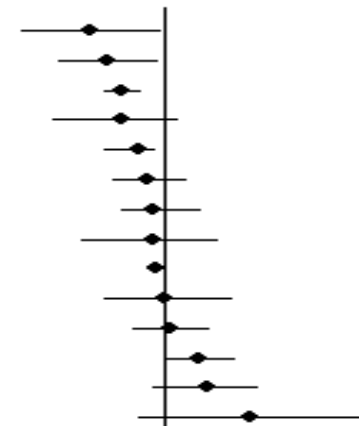
Parent et al, 2011
Lam et al, 2004
Brownson et al, 1991
Andersson et al, 1995
Darlington et al, 2007
Friedenreich et al, 2004
Milleneuve et al, 1999
Putnam et al, 2000
Whittemore et al, 1995
Le Marchand et al, 1991
Wiklund et al, 2008
Sass-Kortsak et al, 2007
Lacey et al, 2001
West et al, 1991

Hospital-based

Jian et al, 2005
Dosemeci et al, 1993
Gallus et al, 2007
Lagiou et al, 2008
Yu et al, 1988
Pierotti et al, 2005
Bairati et al, 2000
Pierotti et al, 2005
Pierotti et al, 2004
Shahar et al, 2011
Chen et al, 2005
Sung et al, 1999

Nested case-control study (within a cohort)

Krishnadasan et al, 2008



Statistically significant risk reductions in 8 of 26 studies (30%)

0.001

0.01

0.125

0.5

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Physical Activity and Risk of Lung Cancer

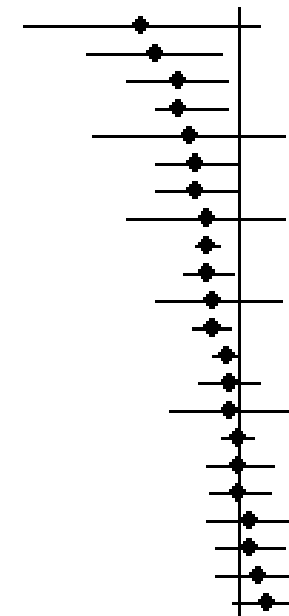
Summary of Evidence on Physical Activity and Lung Cancer Risk

- Consistent evidence (*20 of 28 studies*)
 - ◆ 7 show no effect
 - ◆ 20 show decreased risks
- Fairly strong risk reductions (*25% decreases for highest vs. lowest activity levels*)
- Evidence of dose-response (*9 of 11 studies*)
 - ◆ about half of the studies that examined these trends
- Weaker evidence for biologic plausibility exists
- Effect of smoking needs to be considered

Physical Activity and Lung Cancer: Cohort Studies

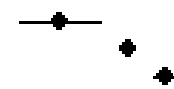
Prospective

Knekt et al, 1996
Sprague et al, 2008 Male
Lee et al, 1999
Lee et al, 1994
Sprague et al, 2008 Female
Severson et al, 1989
Thune et al, 1997
Wannamethee et al, 2001
Leitzmann et al, 2008 Male
Sinner et al, 2008
Steenland et al, 1995
Leitzmann et al, 2008 Female
Bak et al, 2005
Schnohr, 2005
Inoue et al, 2008 Female
Alfano et al, 2004
Steindorf et al, 2006 Recreational, Female
Steindorf et al, 2006 Recreational, Male
Steindorf et al, 2006 Occupational, Female
Inoue et al, 2008 Male
Colbert et al, 2002
Steindorf et al, 2006 Occupational, Male



Retrospective

Pukkala et al, 2000
Paffenbarger et al, 1987
Yun et al, 2008



Statistically significant risk reduction in 7 of 19 studies (37%)

0.001 0.01 0.125 0.5 1 2 4 10

Physical Activity and Lung Cancer: Case-Control Studies

Population-based

Lam et al, 2004
Parent et al, 2011 Overall PA
Parent et al, 2011 Recreational
Mao et al, 2003
Brownson et al, 1991

Hospital-based

Lin et al, 2012
Kubik et al, 2004
Kubik et al, 2008 Ever smokers, Female
Kubik et al, 2008 Ever smokers, Male
Kubik et al, 2008 Never smokers, Male
Kubik et al, 2008 Never smokers, Female
Dosemeci et al, 1993

Statistically significant risk reduction in 6 of 8 studies (75%)

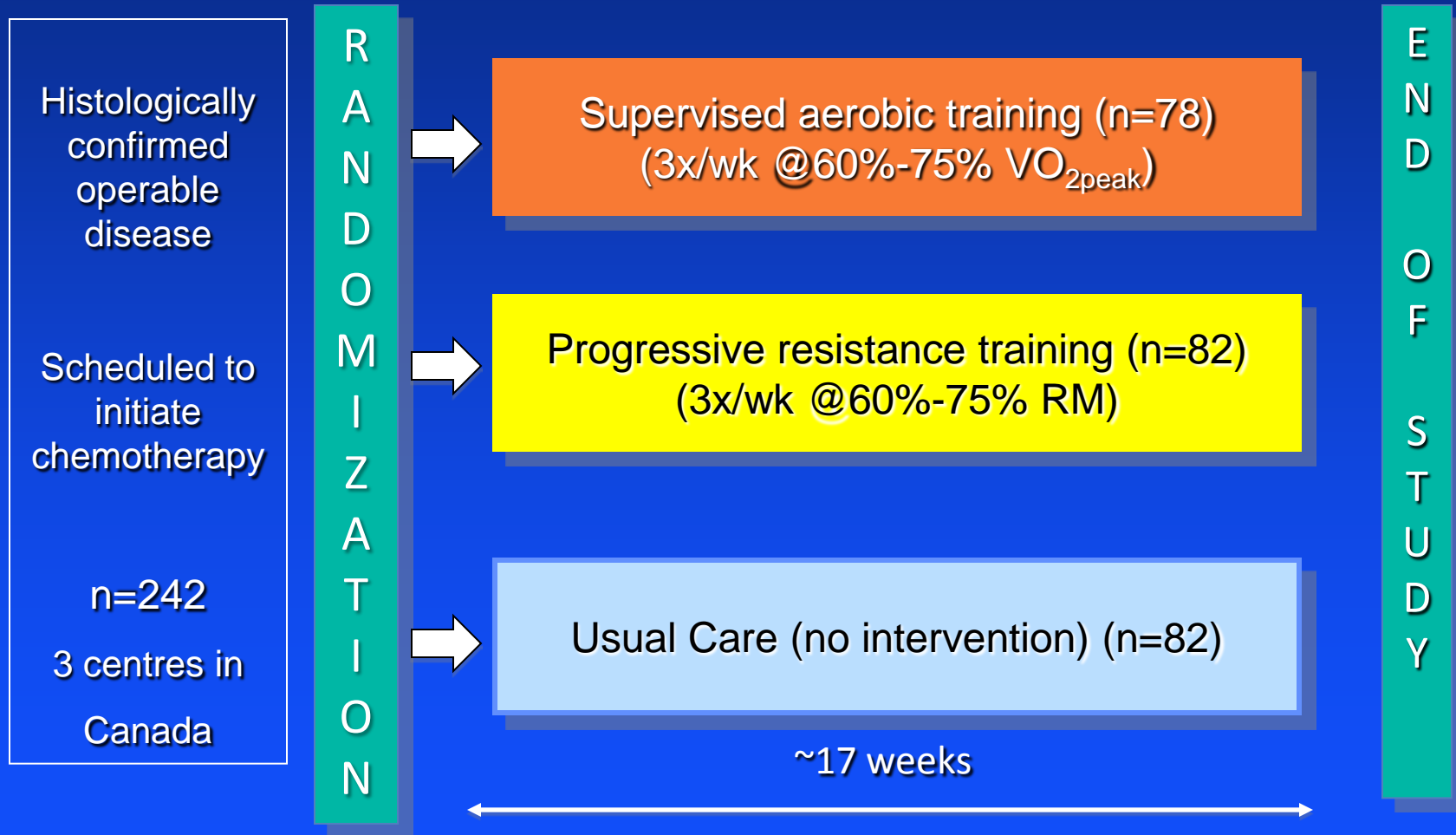
0.001 0.01 0.125 0.5 1 2 4 10

Summary of Evidence on Physical Activity and Cancer Risk by Site

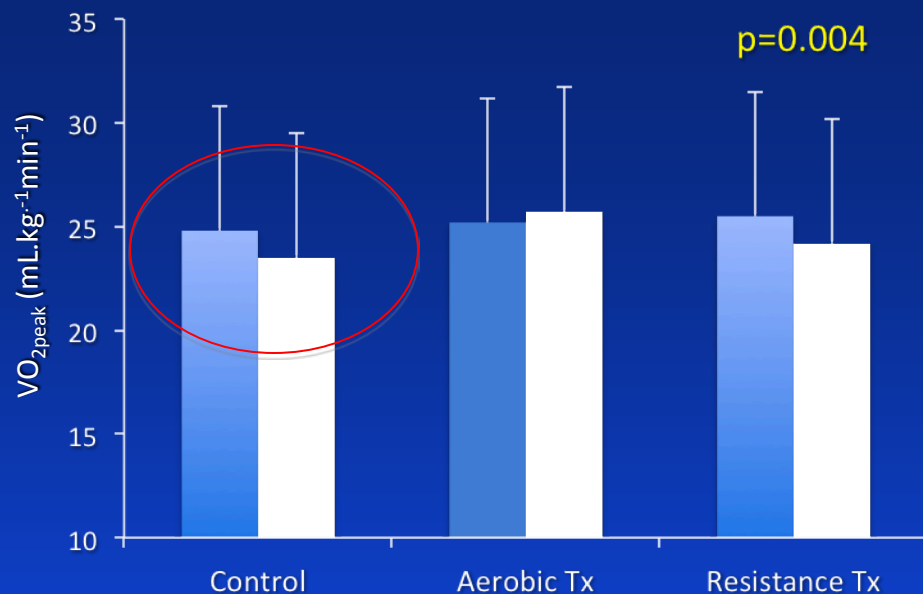
| Cancer Site | Number of Studies | Studies found reduced risk | Consistency of evidence | Magnitude of risk reduction | Dose-response effect |
|-------------|----------------------|----------------------------|-------------------------|-----------------------------|----------------------|
| Colon | 86 | 72 | Yes | 30% | Yes |
| Breast | 88 | 66 | Yes | 25% | Yes |
| Endometrial | 28 | 23 | Yes | 30-35% | Yes |
| Lung | 28 | 20 | Some | 25% | Some |
| Prostate | 56 | 26 | No | 10% | Limited |
| Ovarian | 24 | 12 | No | <10% | Limited |
| All Others | Insufficient or Null | | | | |

Physical Activity During Cancer Treatment

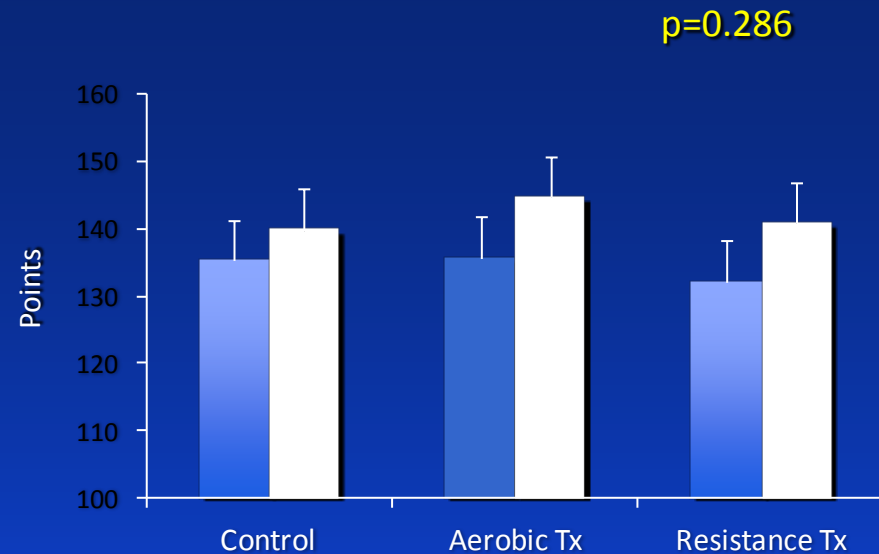
Supervised Trial of Aerobic vs Resistance Training (START Trial)



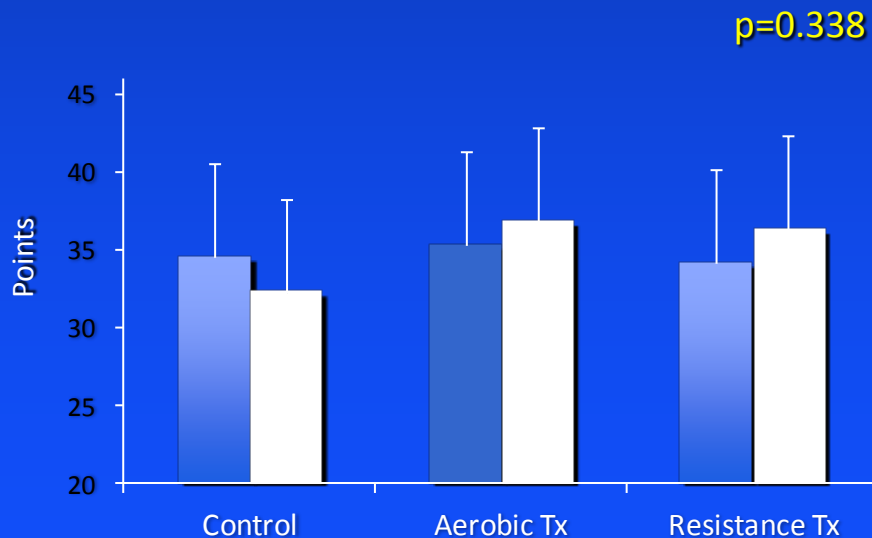
Aerobic capacity



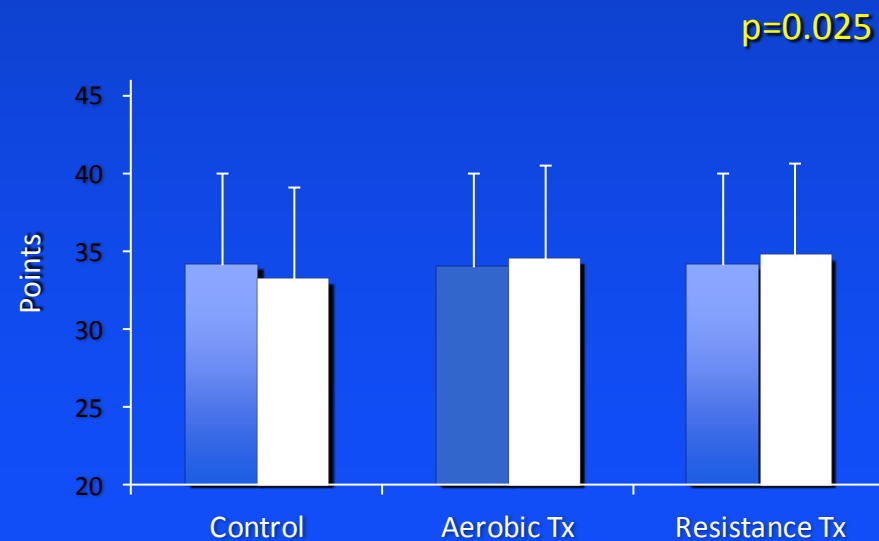
QOL



Fatigue



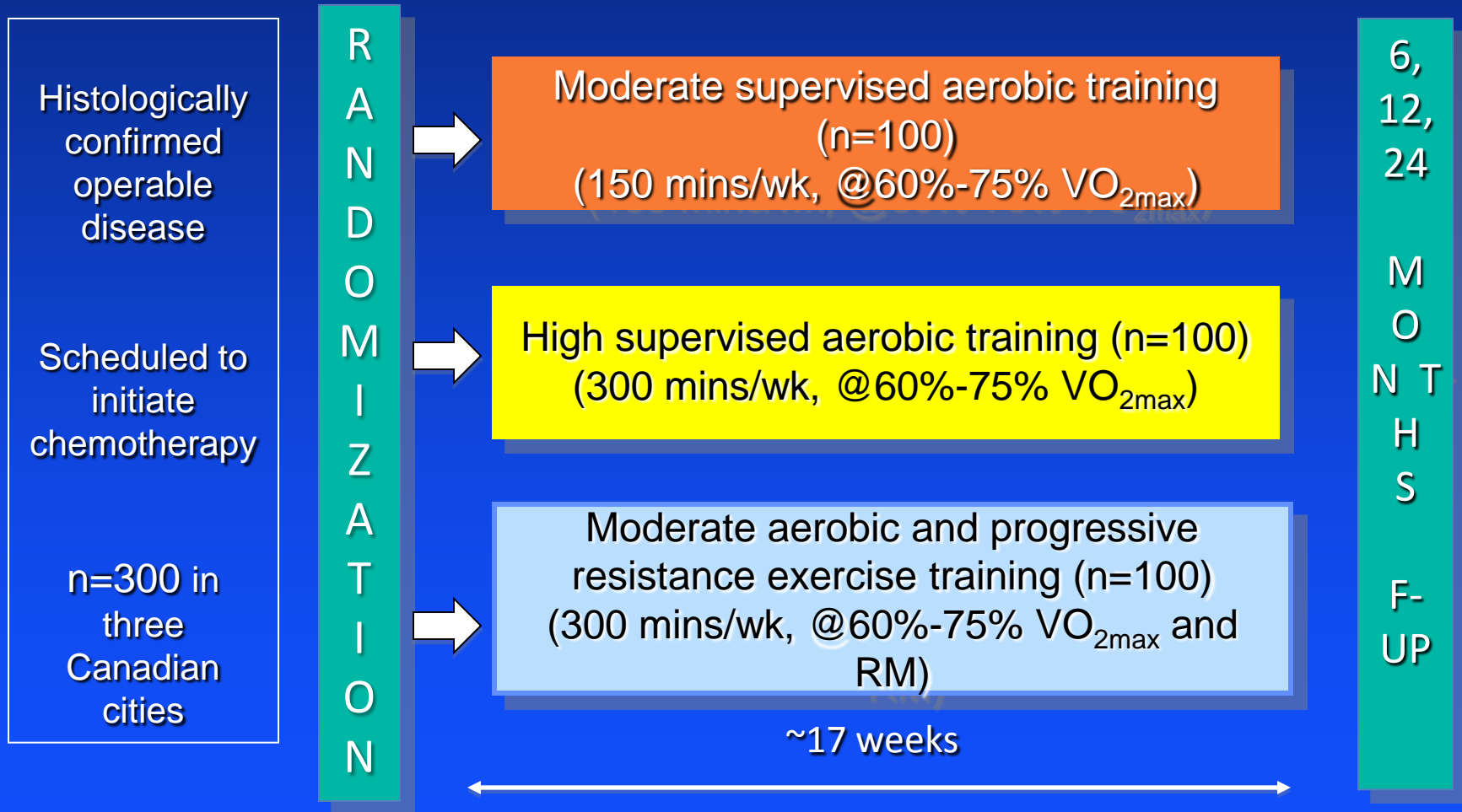
Self-esteem



Main Results from START Trial

- Aerobic exercise (AET) was better than usual care (UC) for:
 - ◆ Self-esteem
 - ◆ Aerobic fitness
 - ◆ Percent body fat
 - ◆ Fat mass
- Resistance exercise (RET) was better than usual care for:
 - ◆ Self-esteem
 - ◆ Lower body strength
 - ◆ Upper body strength
 - ◆ Lean body mass
 - ◆ Chemotherapy completion rate
- Improved quality of life, fatigue, depression and anxiety in exercise groups as compared to usual care (*non-statistically significant improvements*)

Combined Aerobic and Resistance Exercise Trial (CARE Trial)



Randomized Controlled Trials of Physical Activity in Cancer Survivors

Summary of Effects of Exercise on Physical Characteristics By Cancer Phase

| Characteristic | Treatment | | Survivorship | |
|---------------------|-----------|---------|--------------|---------|
| | Effect | P-value | Effect | P-value |
| PA level | ↑ | 0.70 | ↑↑ | 0.0001 |
| Aerobic fitness | ↑ | 0.03 | ↑ | 0.03 |
| Upper body strength | ↑↑ | 0.006 | ↑↑ | 0.0001 |
| Lower body strength | ↑↑ | 0.006 | ↑ | 0.02 |
| Body weight | ↓ | 0.05 | ↓↓ | 0.004 |
| % body fat | ↓ | 0.04 | ↓↓ | 0.006 |

Summary of Effects of Exercise on Patient Reported Outcomes By Cancer Phase

| Characteristic | Treatment | | Survivorship | |
|-------------------|-----------|---------|--------------|---------|
| | Effect | P-value | Effect | P-value |
| Fatigue | ↓ | 0.75 | ↓↓ | 0.003 |
| Quality of life | ↑ | 0.11 | ↑ | 0.03 |
| Physical function | ↑↑ | 0.04 | ↑ | 0.25 |
| Depression | Null | 0.70 | ↓ | 0.10 |
| Anxiety | ↓ | 0.02 | ↓↓ | 0.07 |

Observational Studies on Physical Activity and Breast Cancer Survival

Ballard-Barbash et al. JNCI 2012; 104: 815-840

Physical Activity and Breast Cancer Mortality: Observational Studies

Randomized Controlled Trial Follow-up

Bertram, 2011

Prospective Cohort

Hellmann, 2010

Borugian, 2004

Emaus, 2010

Holmes, 2005

Irwin, 2011

Chen, 2011

West-Wright, 2009

Cancer Survivorship Cohort

Stemfeld, 2009

Irwin, 2008

Multi-centered Case-control Study Follow-up

Dal Maso, 2008

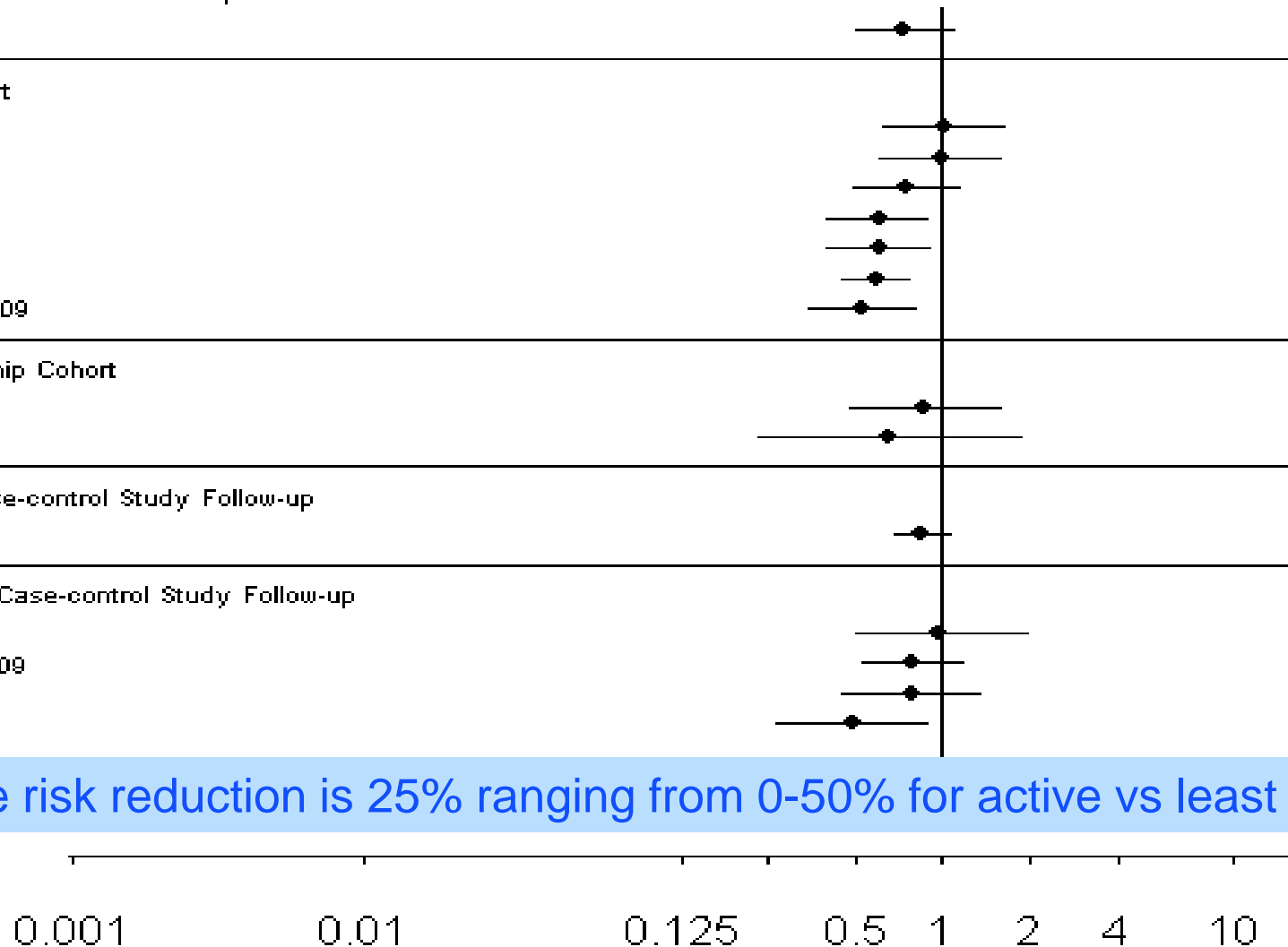
Population-Based Case-control Study Follow-up

Rohan, 1995

Friedenreich, 2009

Enger, 2004

Holick, 2008



Average risk reduction is 25% ranging from 0-50% for active vs least active

Physical Activity and Breast Cancer

Observational Studies: All Cause Mortality

Randomized Controlled Trial Follow-up

Bertram, 2011

Prospective Cohort

Hellmann, 2010

Keegan, 2010

Abrahamson, 2006

Emaus, 2010

West-Wright, 2009

Holmes, 2005

Chen, 2011

Irwin, 2011

Cancer Survivorship Cohort

Stemfeld, 2009

Irwin, 2008

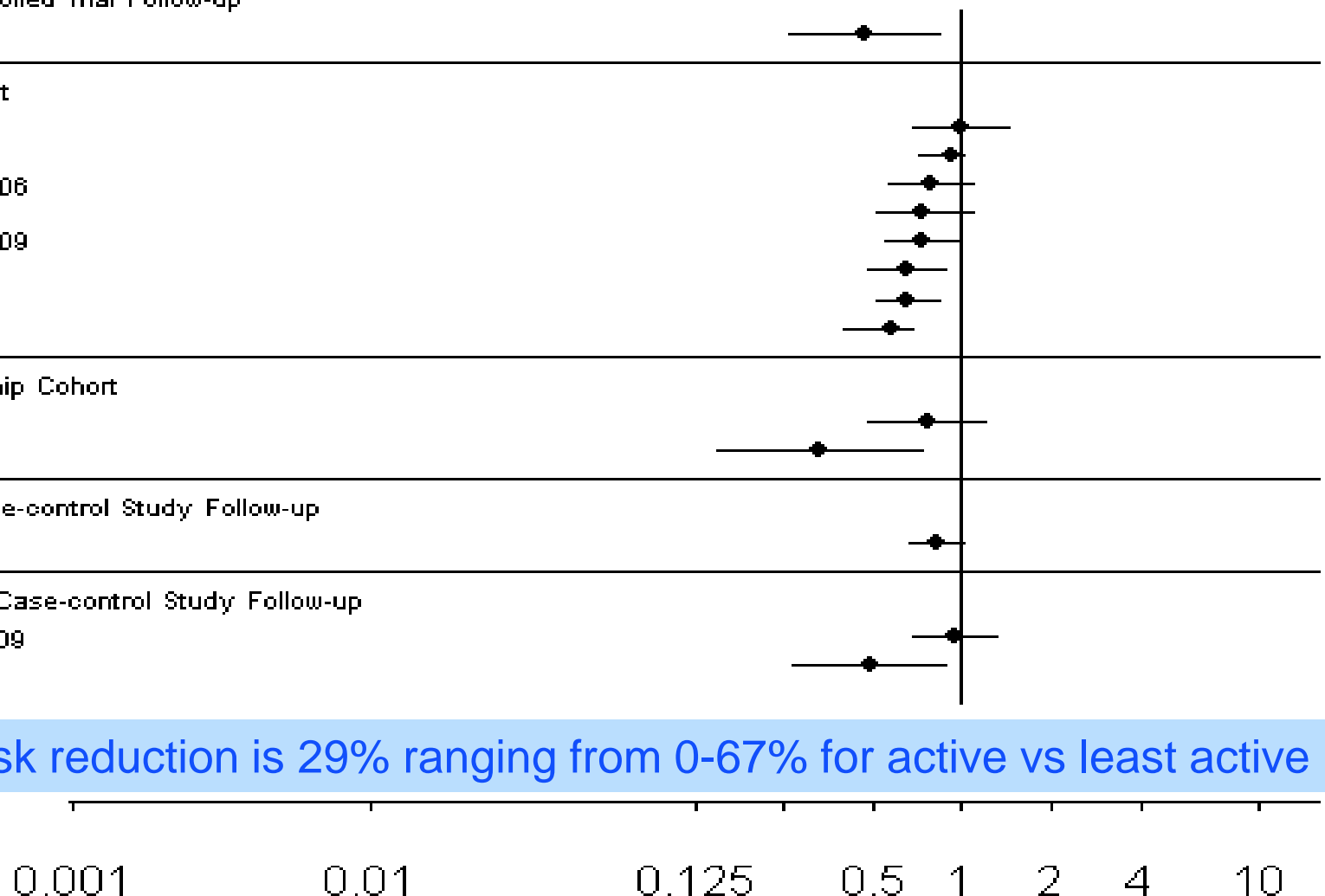
Multi-centered Case-control Study Follow-up

Dal Maso, 2008

Population-Based Case-control Study Follow-up

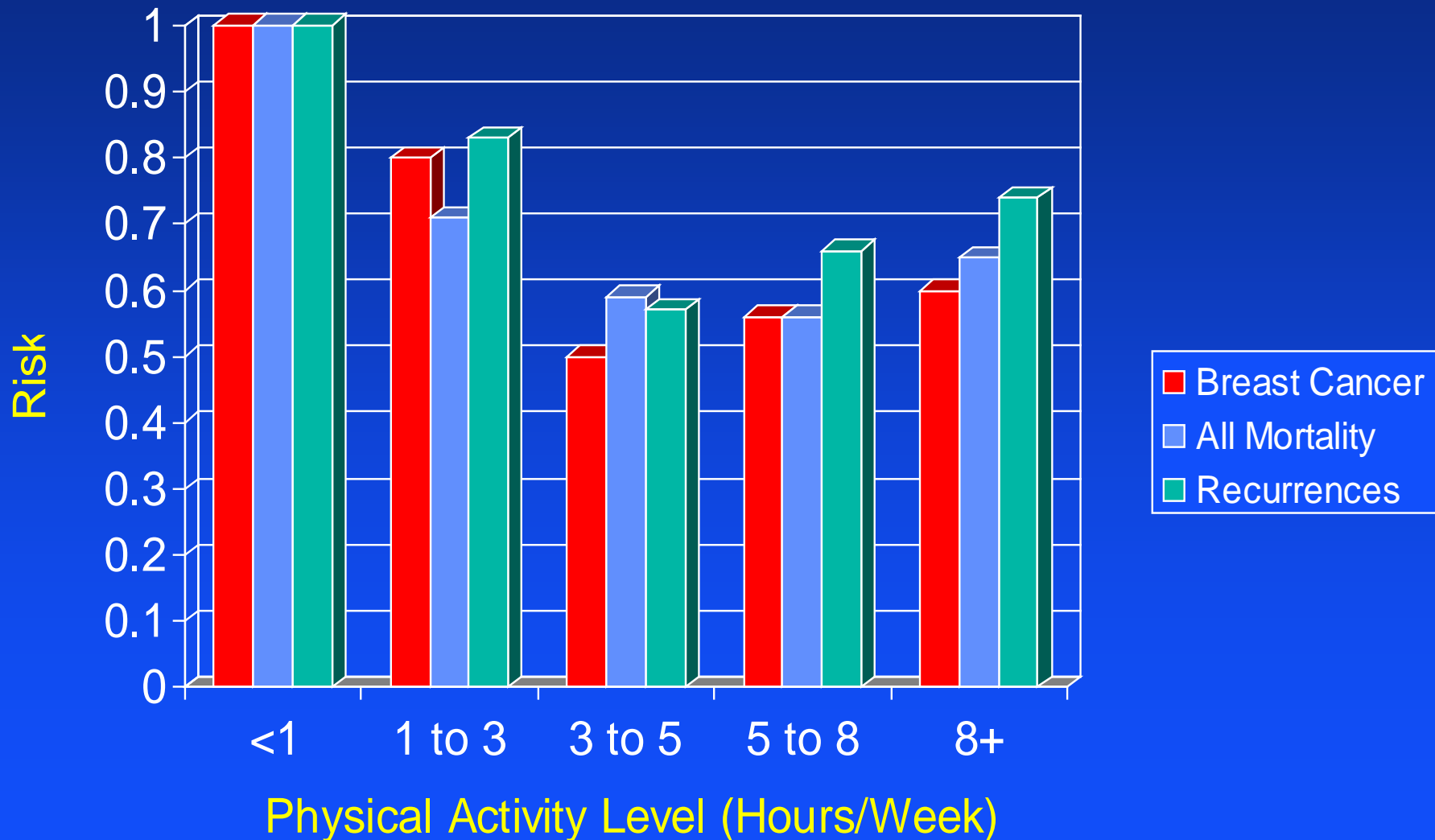
Friedenreich, 2009

Holick, 2008

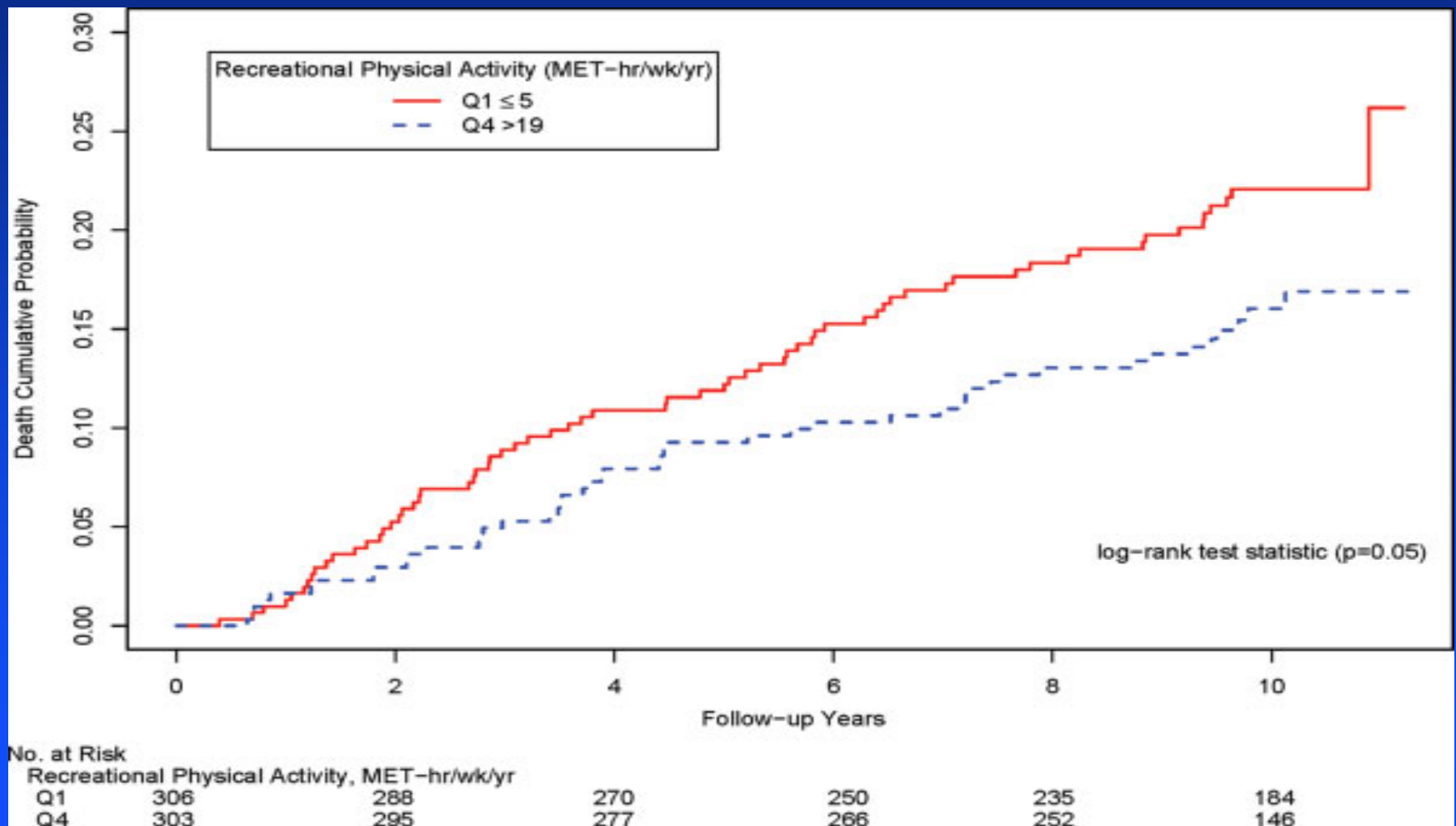


Average risk reduction is 29% ranging from 0-67% for active vs least active

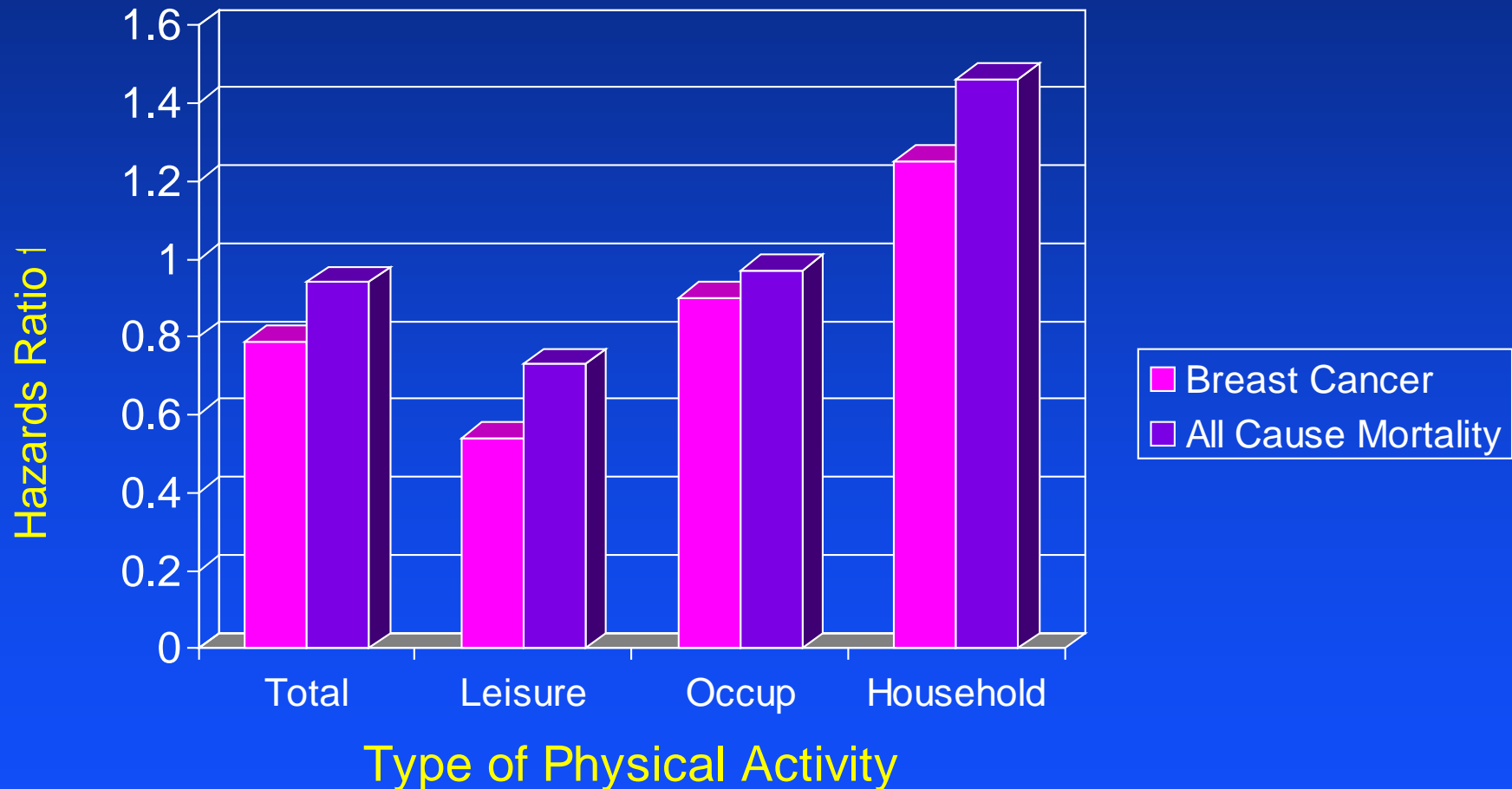
Risk of Breast Cancer Recurrence and Mortality by Physical Activity Level



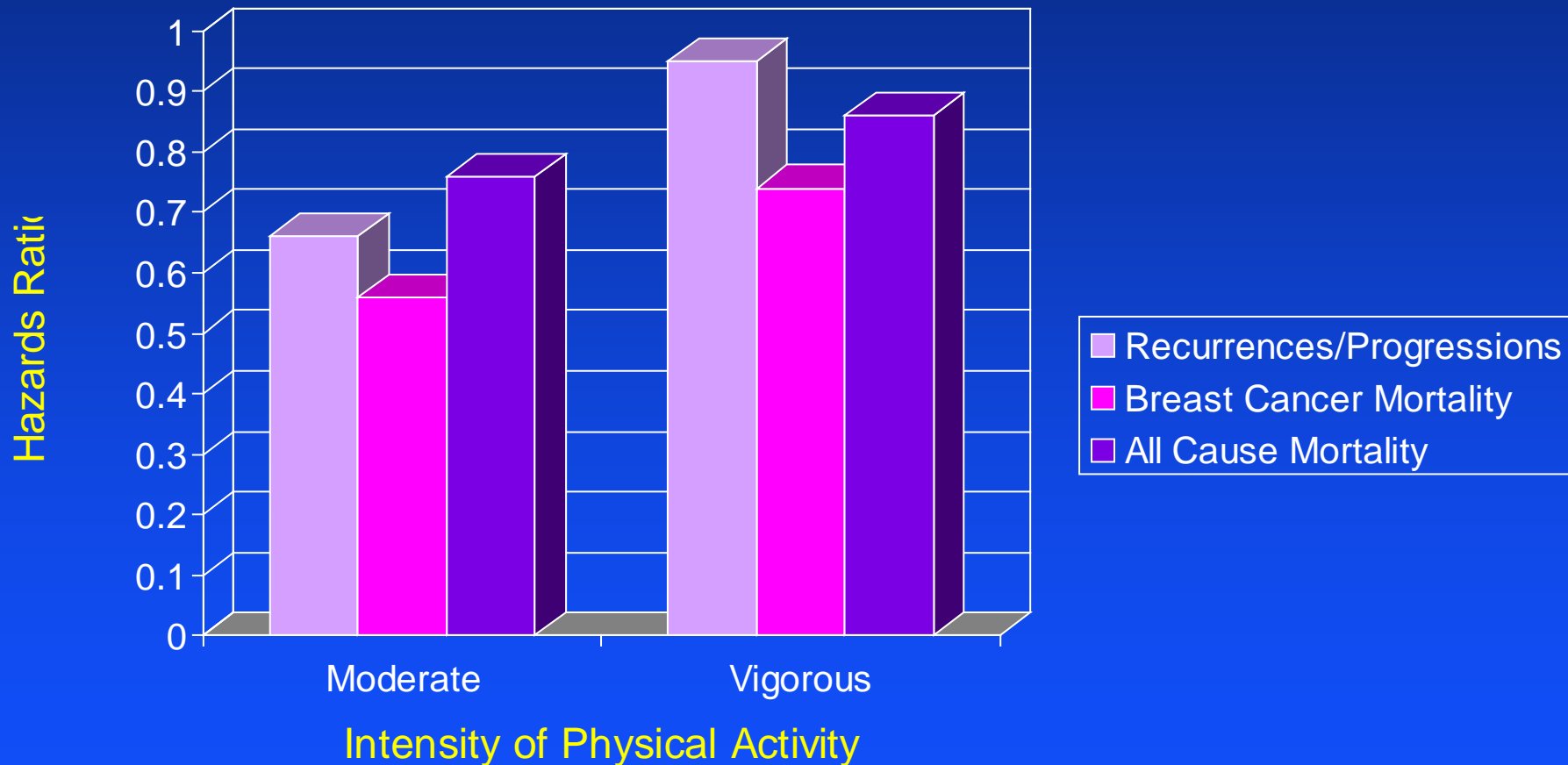
Alberta Cohort Study of Lifetime PA and Breast Cancer Survival



Alberta Cohort Study of Lifetime PA and Breast Cancer Survival

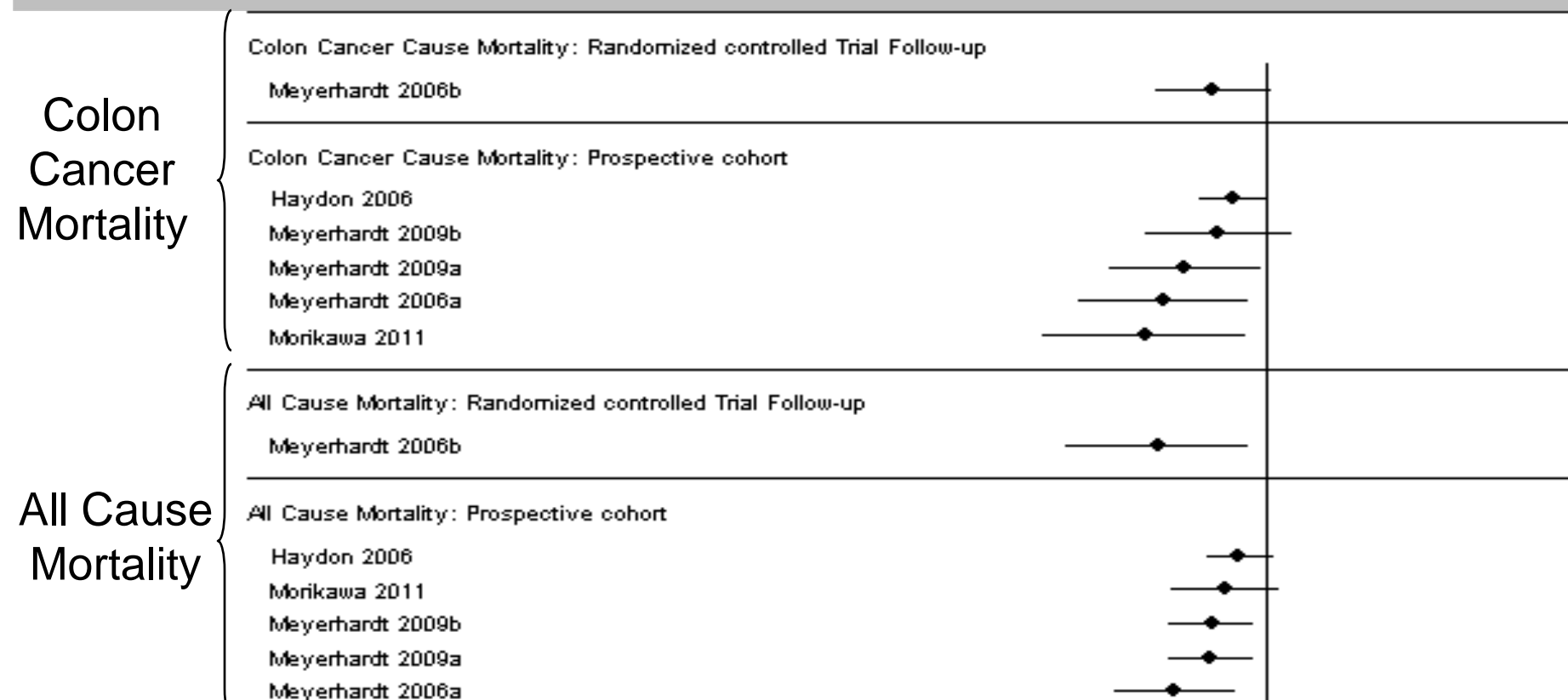


Alberta Cohort Study of Lifetime PA and Breast Cancer Survival



Observational Studies on Physical Activity and Colon Cancer Cancer Survival

Physical Activity and Colon Cancer Mortality and All Cause Mortality: Observational Studies



Average risk reduction is 48% (27-67%) for colon cancer mortality and 44% (23-63%) for all cause mortality for most vs. least active

0.001 0.01 0.125 0.5 1 2 4 10

Nurses Health Study: Survival After Colorectal Cancer by Level of Post-diagnosis Physical Activity

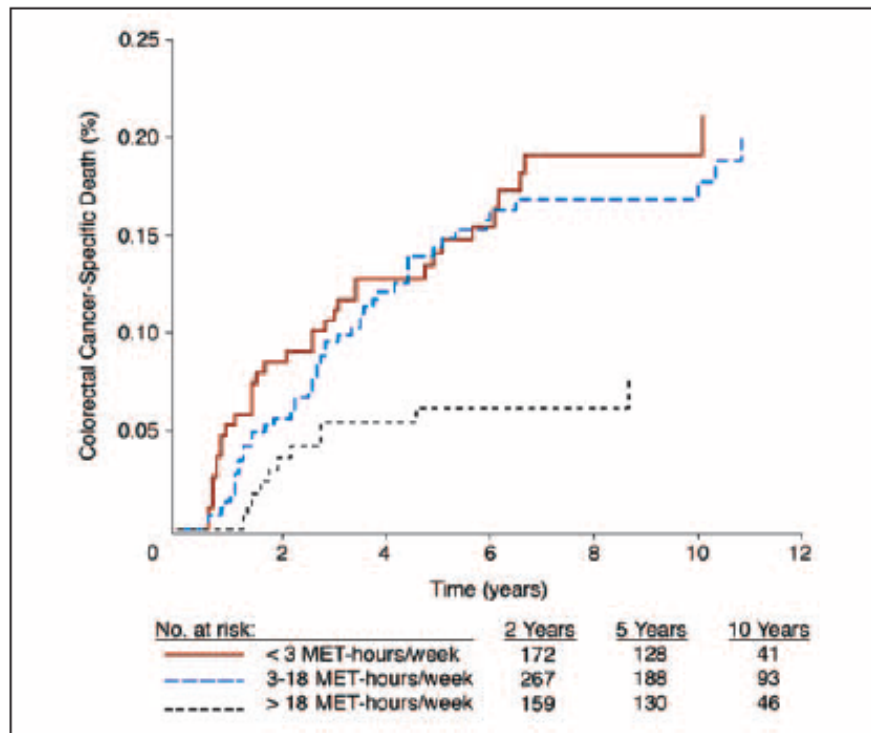


Fig 1. Cumulative incidence curve of colorectal cancer-specific deaths by level of postdiagnosis physical activity. MET, metabolic equivalent task.

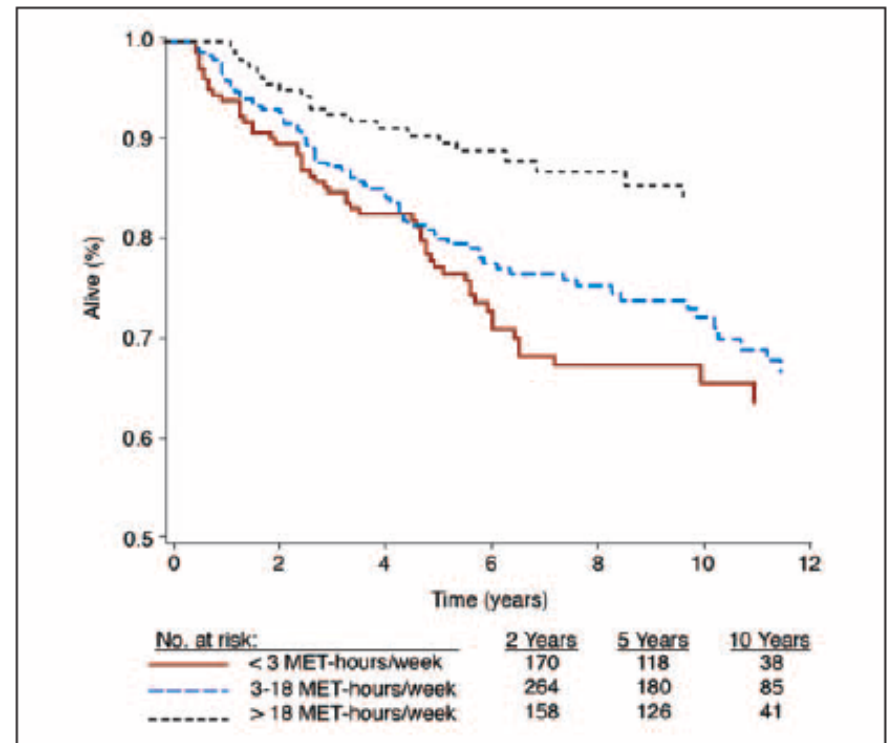
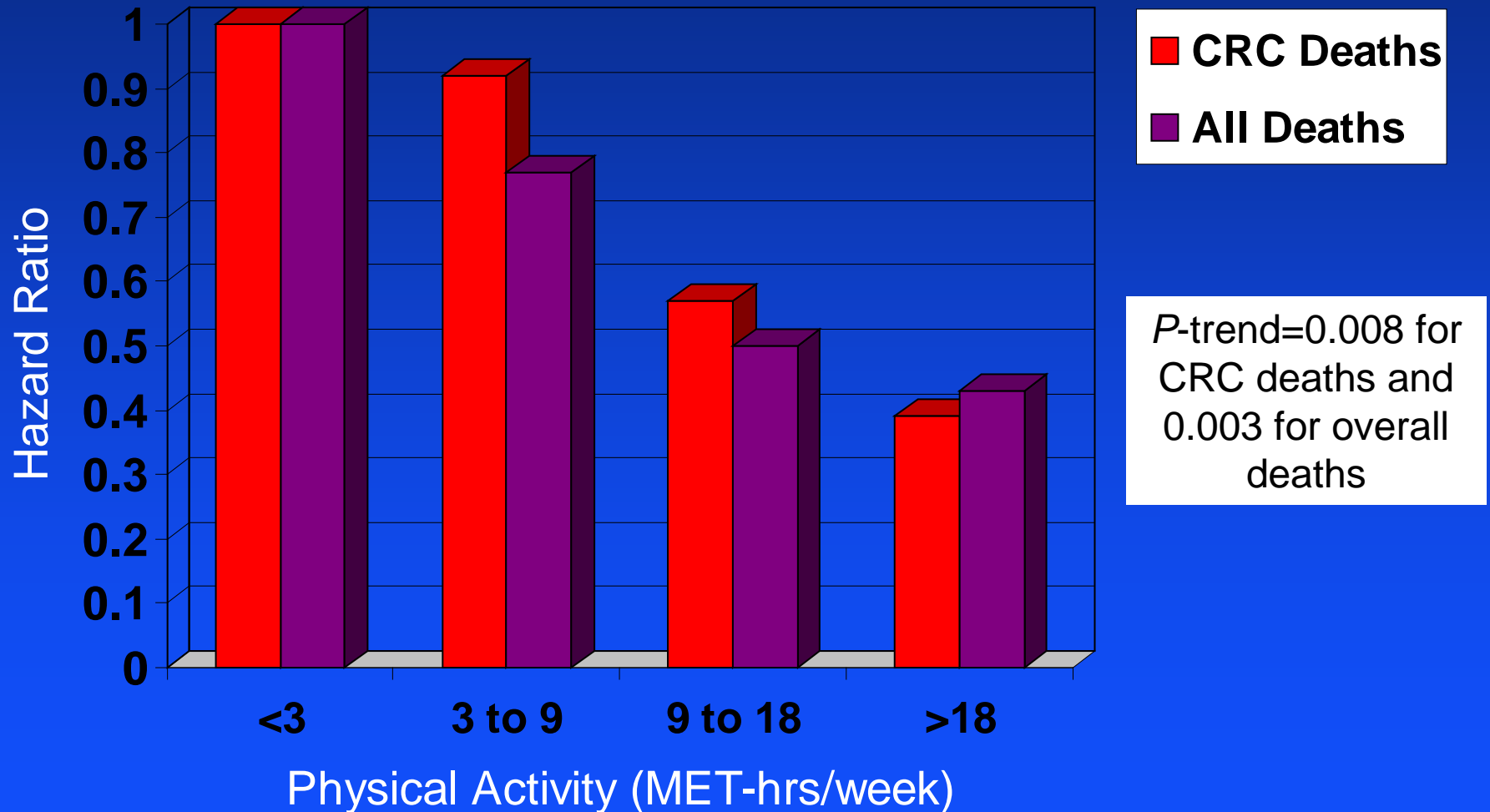


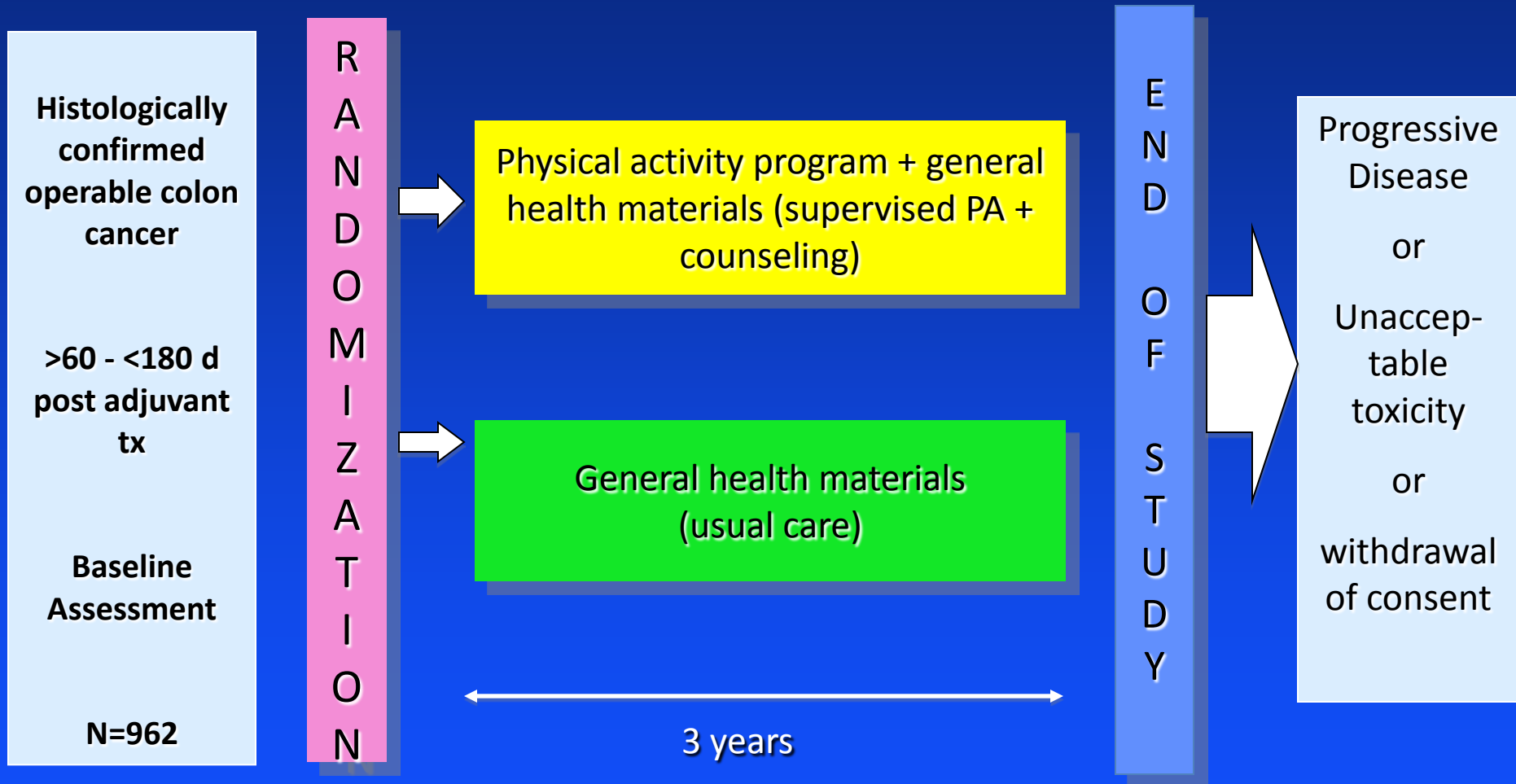
Fig 2. Kaplan and Meier curve of overall survival by level of postdiagnosis physical activity. MET, metabolic equivalent task.

Cumulative incidence and Kaplan-Meier survival curves

Multivariate-Adjusted Hazard Ratios of CRC Specific and Overall Mortality (n=554)



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

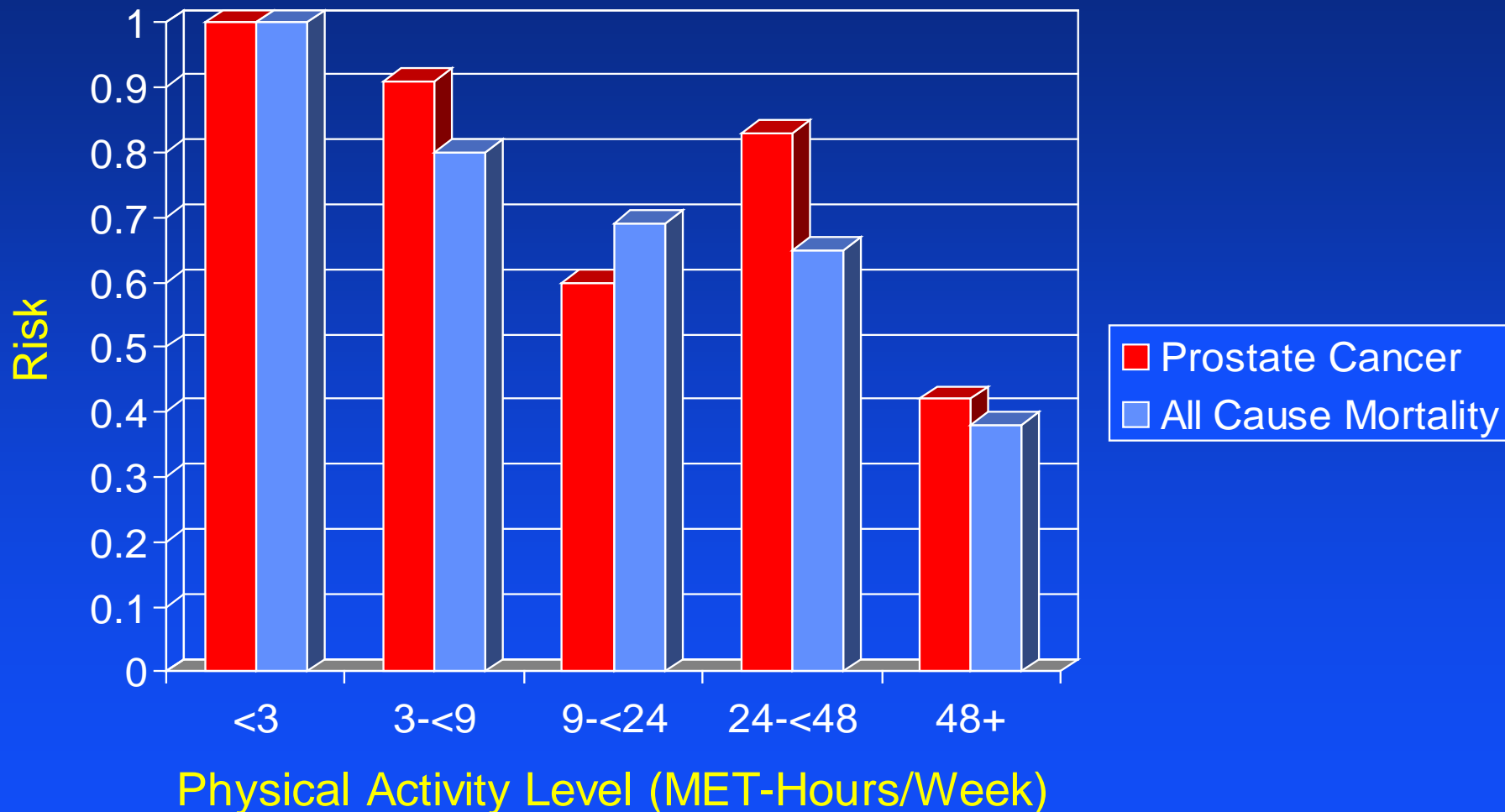


Primary: disease-free survival

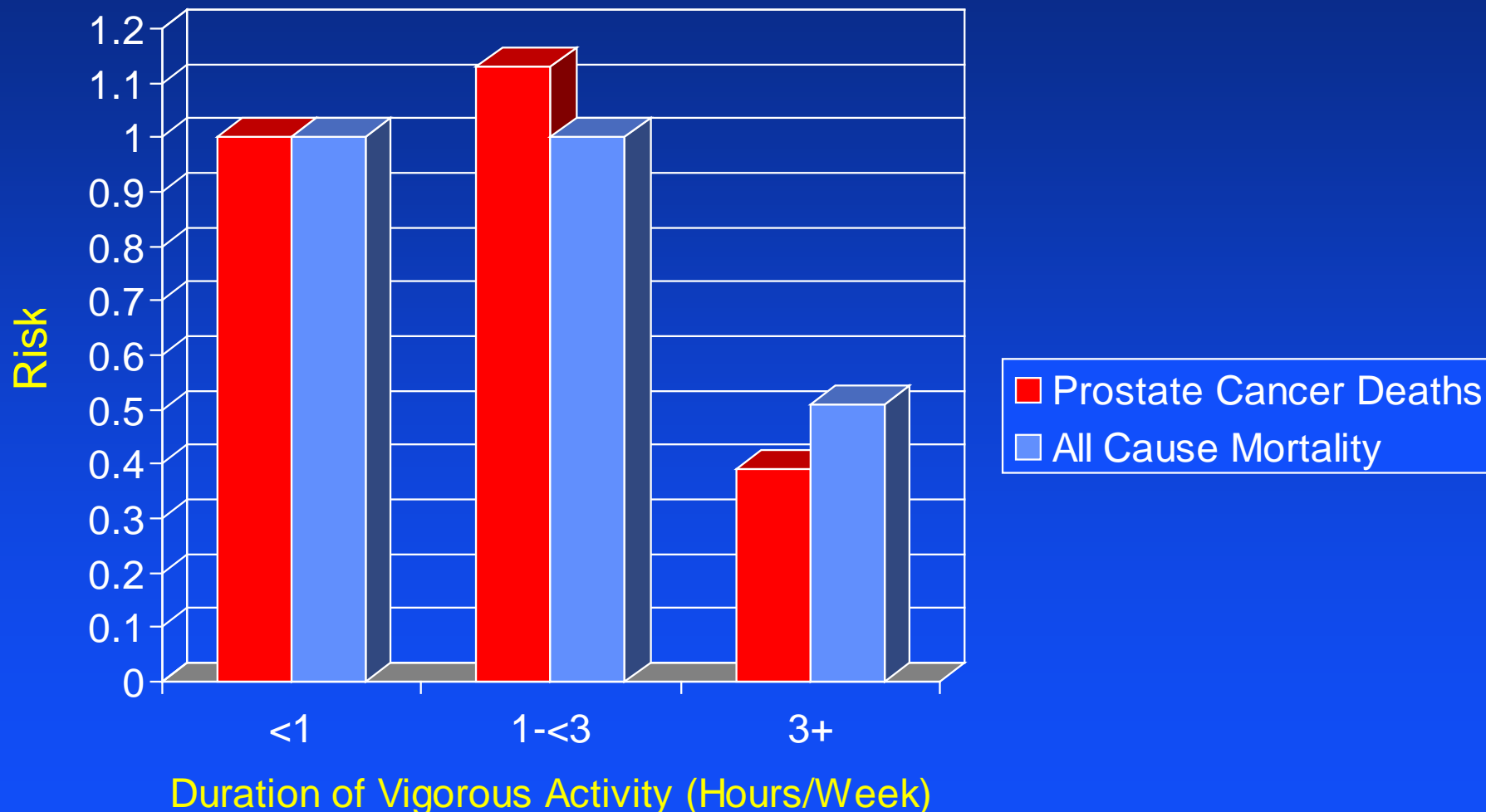
Secondary: PROs, functional capacity, etc.

Physical Activity and Prostate Cancer Survival

Risk of Prostate Cancer Mortality by Post-diagnosis PA



Risk of Prostate Cancer and All Cause Mortality by Vigorous Post-diagnosis Physical Activity



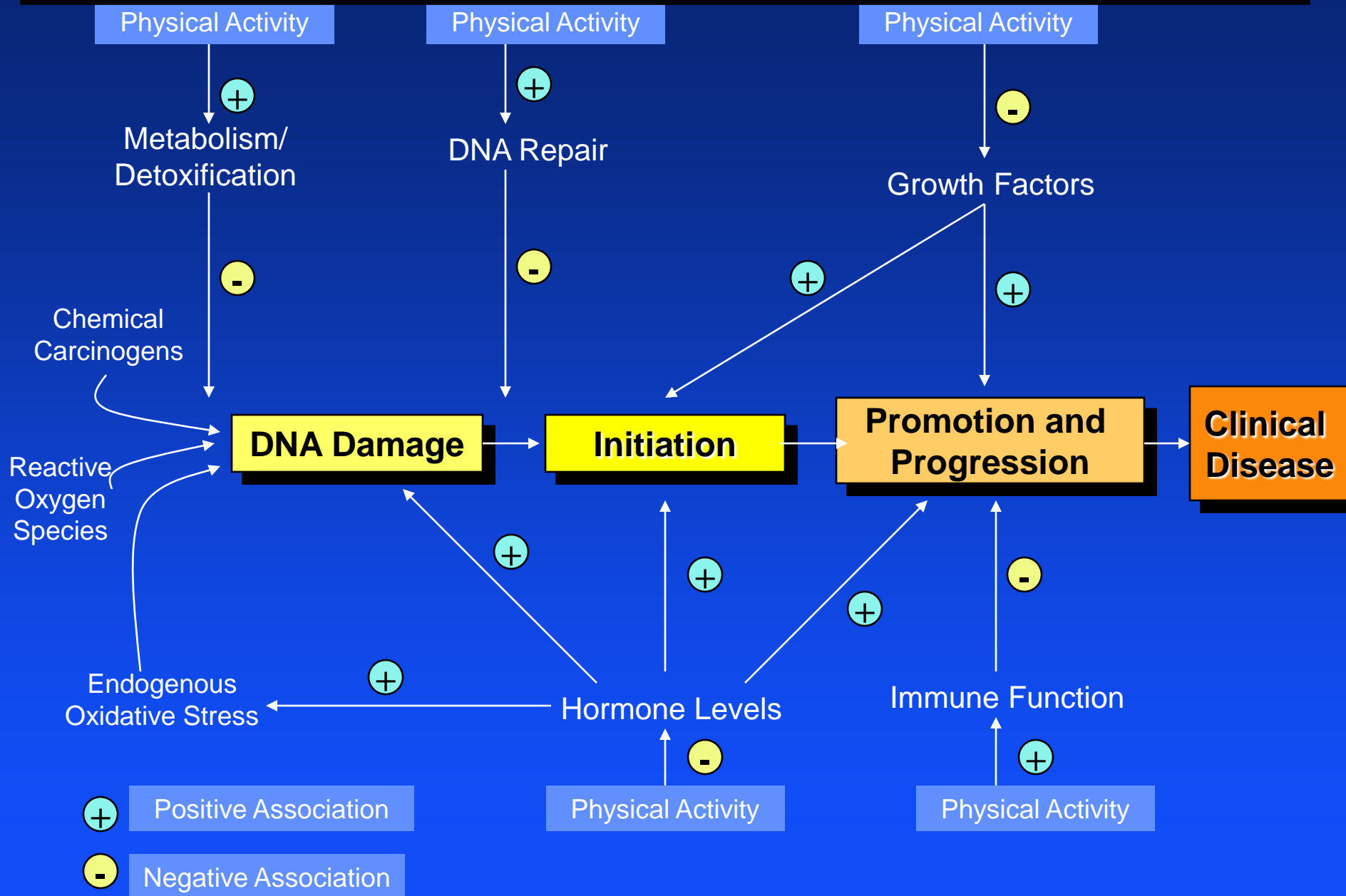
Summary of Evidence on Physical Activity and Cancer Mortality by Site

| Cancer Site | Number of studies | Magnitude of reduction in cancer specific mortality | Magnitude of reduction in all cause mortality | Dose-response effect |
|-------------|-------------------|---|---|----------------------|
| Breast | 17 | 25% | 30% | Some |
| Colon | 6 | 45-50% | 40-45% | Some |
| Prostate | 1 | 60% | 45% | NA |
| Ovarian | 2 | 10%* | 10% | NA |
| Glioma | 1 | NR | 55% | NA |

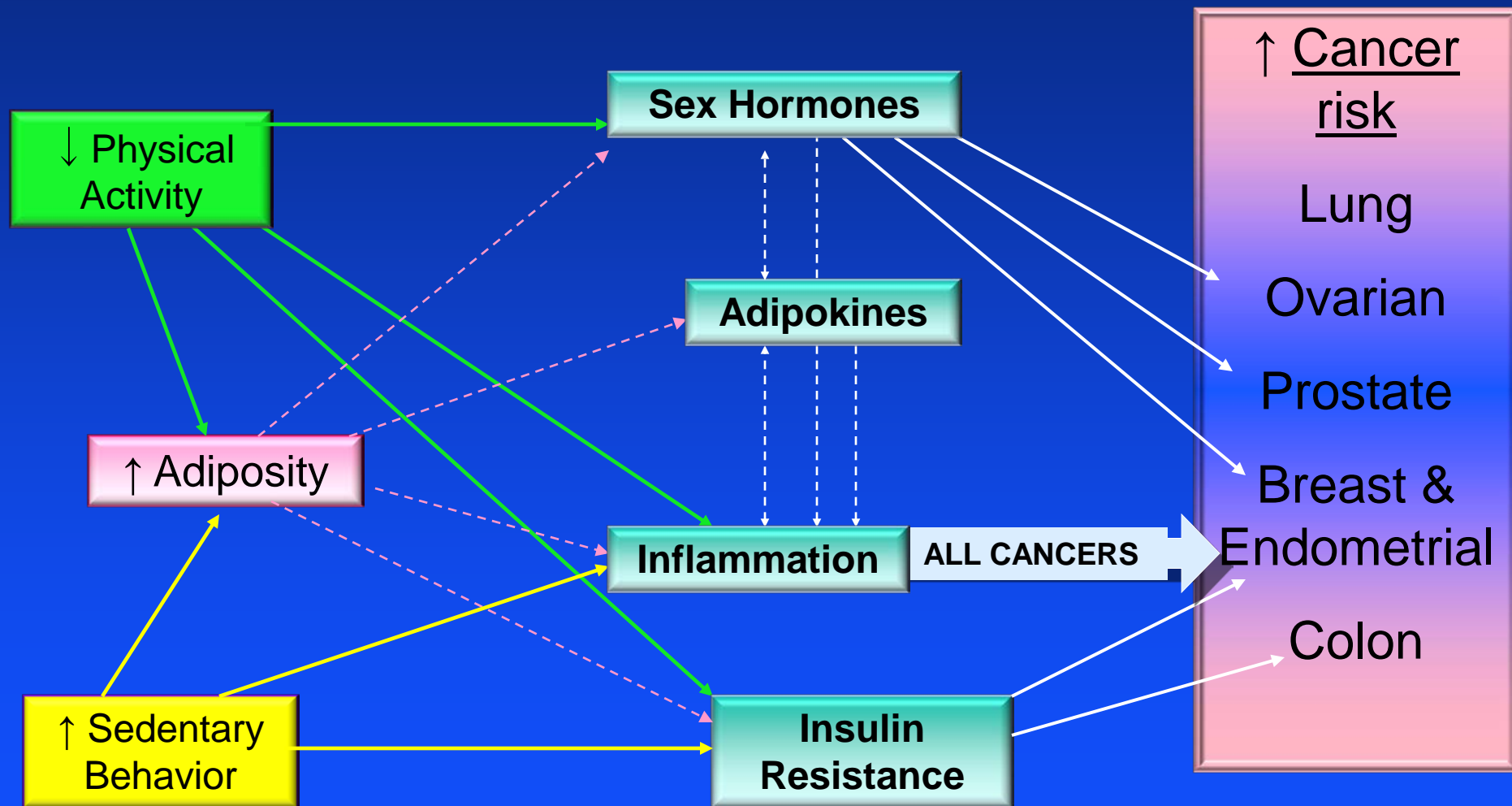
* Increased risk

Physical Activity and Cancer Risk: Biologic Mechanisms

How physical activity could interact with carcinogenesis



Hypothesized Biologic Mechanisms Between Physical Inactivity, Sedentary Behaviour and Cancer Risk



Biologic Mechanisms: Emerging Evidence of Effect of PA

| Mechanism | Possible effect of Physical Activity | Cancer Sites |
|---|---|---|
| Vitamin D | <ul style="list-style-type: none"> Associated with higher 25-hydroxyvitamin D blood levels | Colon, Breast |
| Insulin-like growth factors | <ul style="list-style-type: none"> Might ↓ IGF-1 and ↑ IGFBP-3 | Colon, Premenopausal breast, Endometrium, Ovaries, Prostate, Lung |
| Immune function | <ul style="list-style-type: none"> May improve innate and acquired immune responses to recognize and eliminate cancer cells Effects of long-term, moderate intensity PA on humans at risk not well understood | Most cancers |
| Oxidative stress, anti-oxidant defense and DNA repair | <ul style="list-style-type: none"> May reduce oxidative stress, increase anti-oxidant enzymes (e.g. superoxide dismutase), and/or enhance DNA repair | Most cancers |
| Prostaglandins | <ul style="list-style-type: none"> May inhibit synthesis of prostaglandins | Colon |
| Gastrointestinal transit time | <ul style="list-style-type: none"> ↑ Gut motility and may ↓ transit time → less interaction between mucosa and carcinogens but changes may not be large enough to alter risk | Colon |
| Pulmonary function | <ul style="list-style-type: none"> ↓ Concentration of carcinogens in lung and ↓ exposure time of carcinogens to lung tissue | Lung |



Randomized Controlled Exercise Intervention Trials for Breast Cancer Prevention

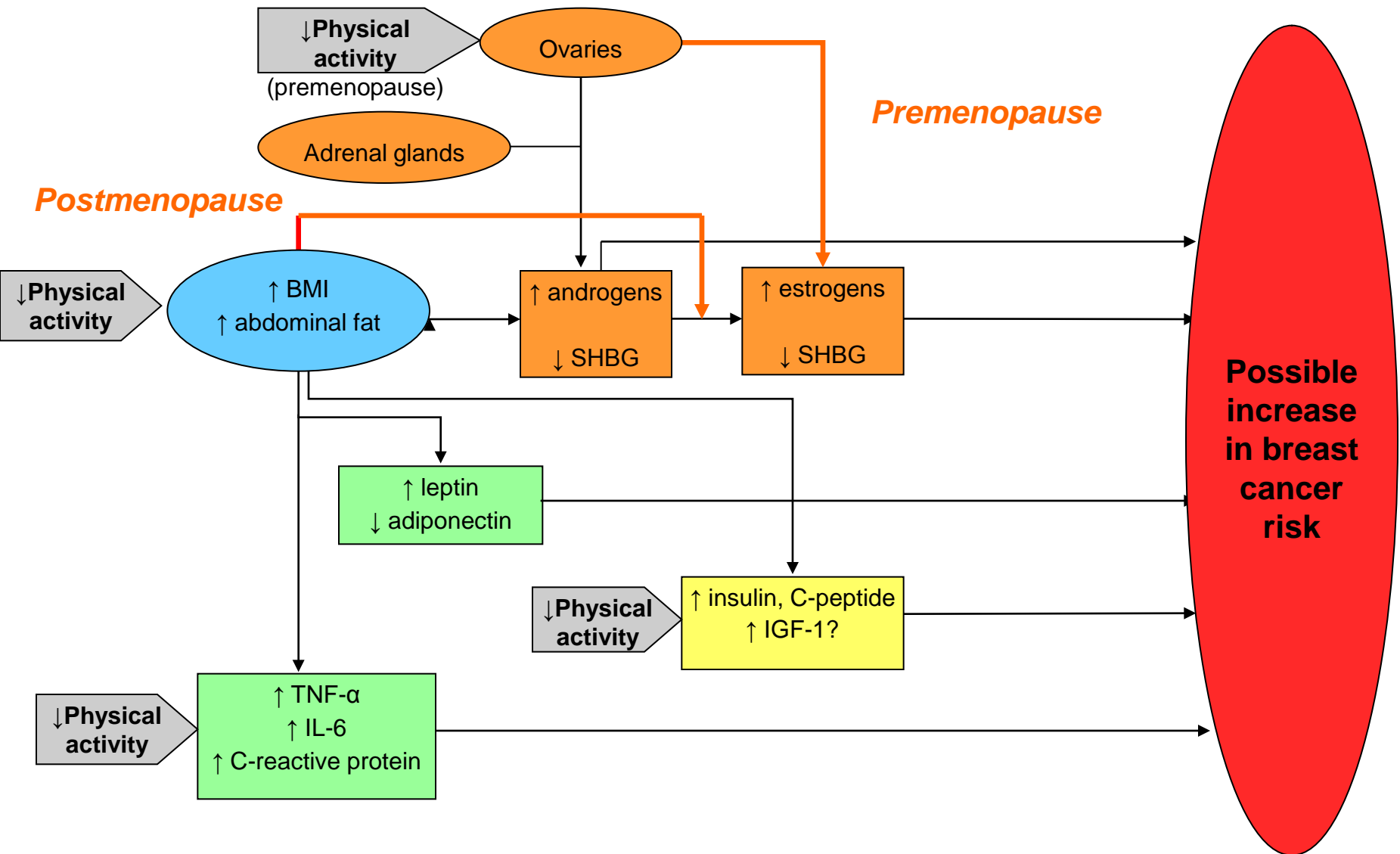
- Three year-long RCTs conducted to date on aerobic exercise and breast cancer biomarkers among postmenopausal, inactive, 50-75 yr old healthy women:
 - ◆ McTiernan et al. (Physical Activity for Total Health Trial) (N=173)
 - ◆ Monninkhof et al. (Sex Hormones and Physical Exercise Trial) (N=189)
 - ◆ Friedenreich et al. (Alberta Physical Activity and Breast Cancer Prevention Trial) (N=320)

ALPHA Trial: Design

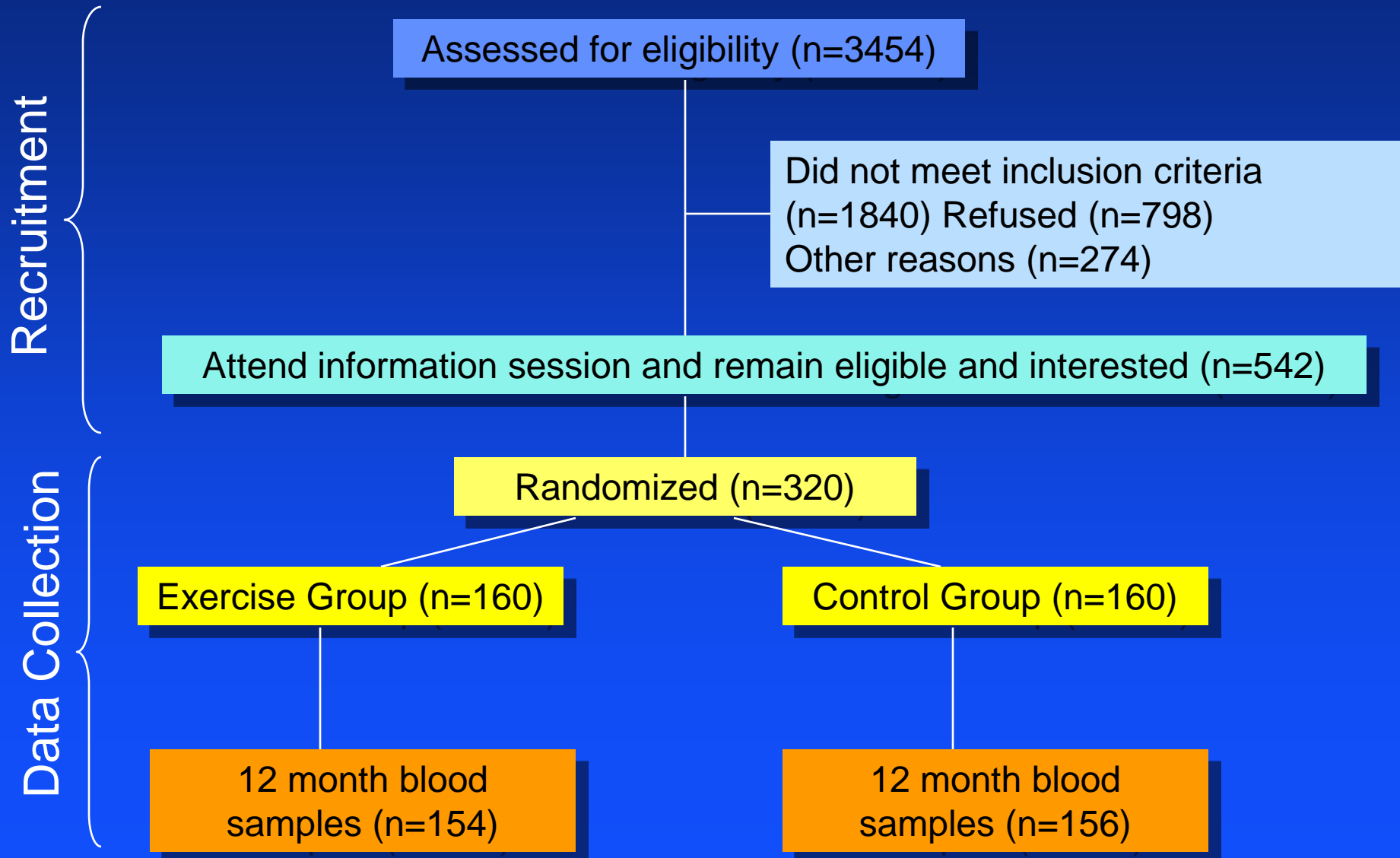
- **Study design:** Two-armed, two-centered RCT
- **Intervention:** Year-long, 5 days/week, 45 mins/session (3 supervised, 2 unsupervised), aerobic exercise only, no change in diet
- **Eligibility criteria:** Postmenopausal, 50-74 yrs, no previous cancer, healthy, BMI=22-40, no HRT use, non-smoker, non-excessive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



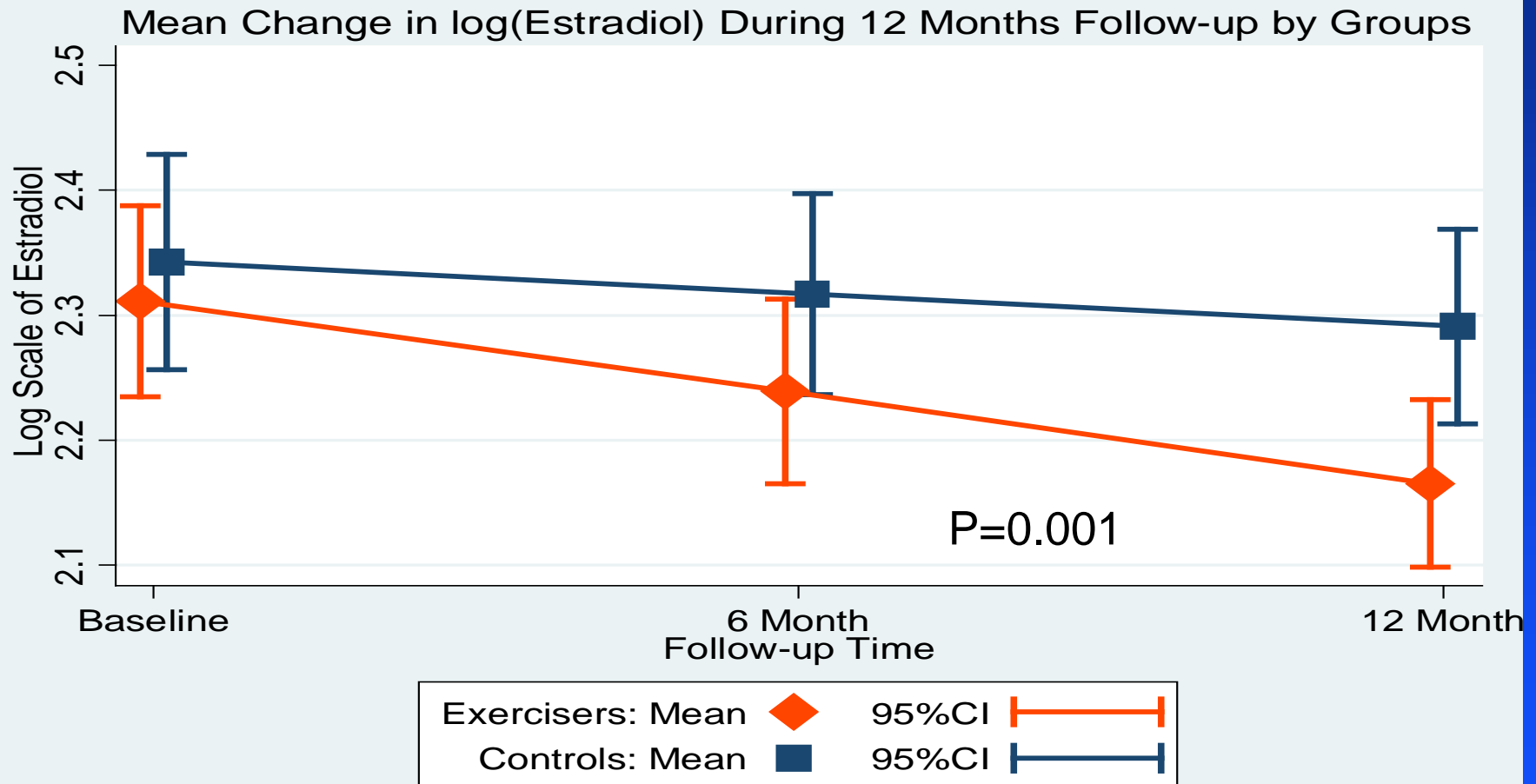
Hypothesized Biologic Mechanisms Between Physical Activity and Breast Cancer



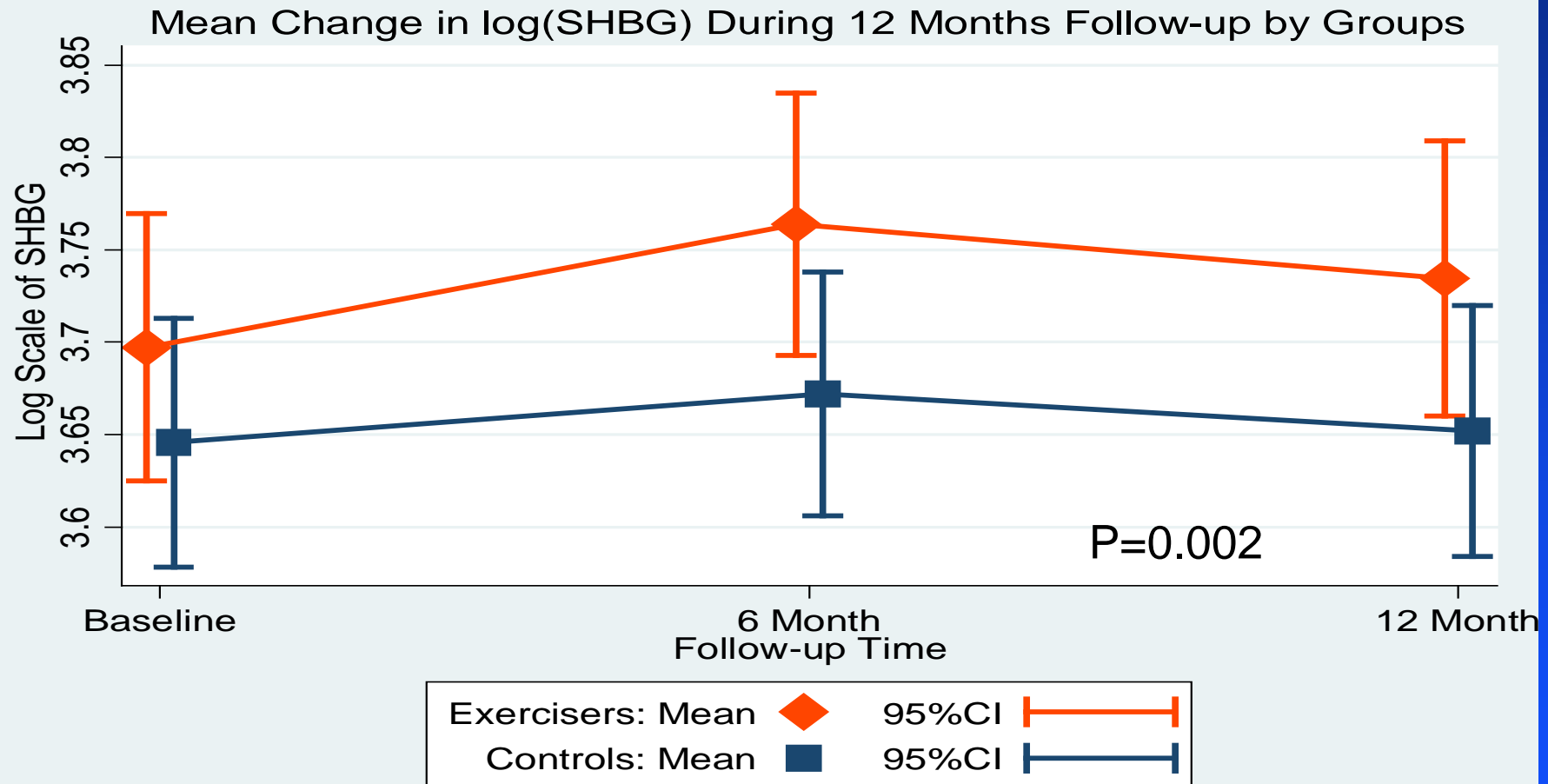
ALPHA Trial: Flow Chart



Impact of Exercise Intervention on Endogenous Estrogens: Estradiol



Impact of Exercise Intervention on Sex Hormone Binding Globulin



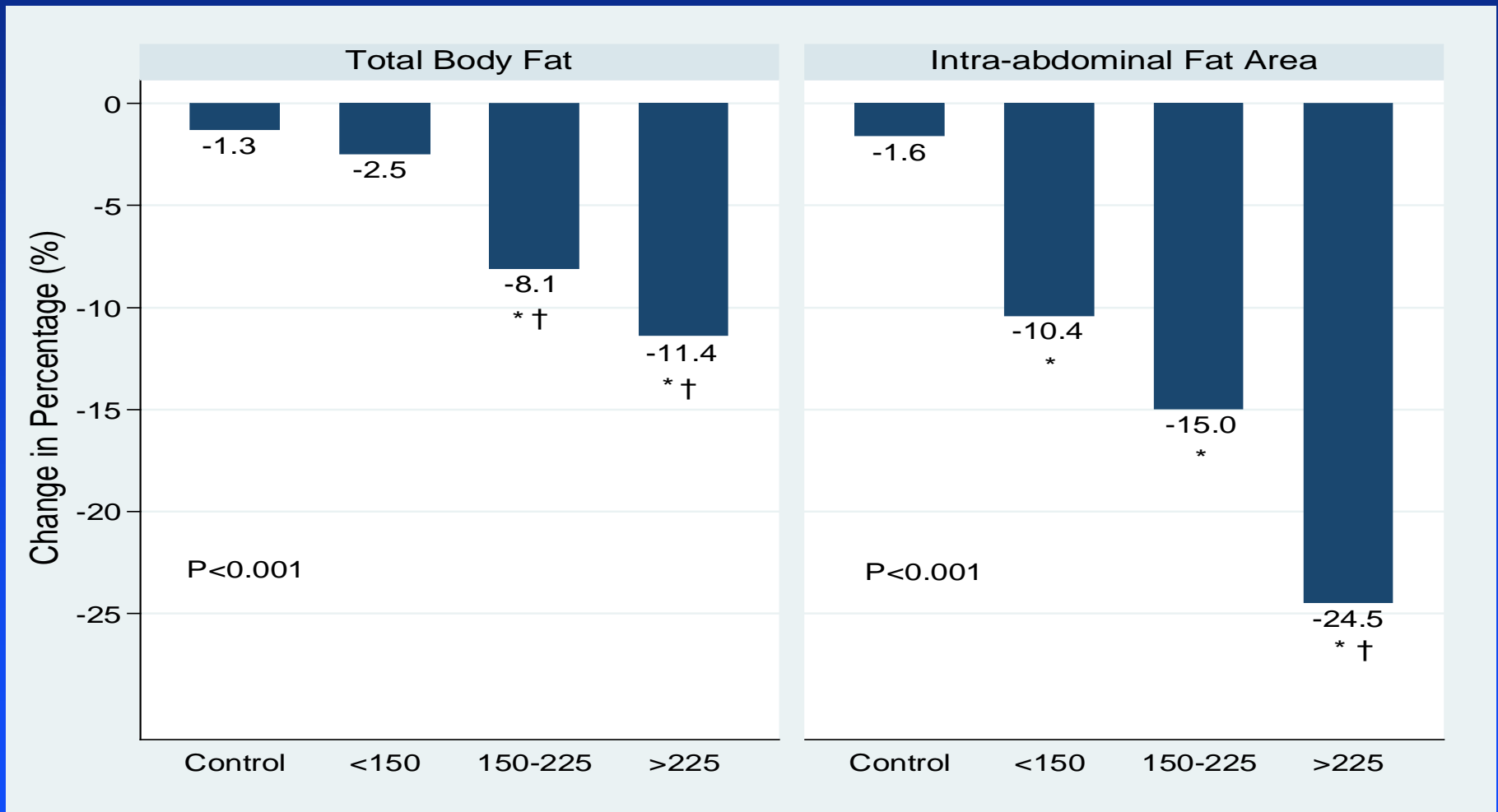
Impact of Exercise Intervention on Adiposity Outcomes

| Change from Baseline | Exercisers | Controls | Difference | <i>p</i> -value |
|---|------------|----------|------------|-----------------|
| Weight (kg) | -2.3 | -0.5 | -1.8 | <.001 |
| Body mass index (kg/m ²) | -0.9 | -0.2 | -0.7 | <.001 |
| Waist circumference (cm) | -2.2 | 0.1 | -2.3 | <.001 |
| Abdominal fat area (cm ²) | -48.5 | -9.6 | -38.9 | <.001 |
| Intra-abdominal fat area (cm ²) | -16.5 | -1.6 | -14.9 | <.001 |

Impact of Exercise Intervention on Adiposity Outcomes

| Change from Baseline | Exercisers | Controls | Difference | <i>p</i> -value |
|--|------------|----------|------------|-----------------|
| Subcutaneous fat area (cm ²) | -32.0 | -7.9 | -24.1 | <.001 |
| Percent body fat | -2.0 | -0.2 | -1.8 | <.001 |
| Fat mass (kg) | -2.4 | -0.4 | -2.0 | <.001 |
| Lean muscle mass (kg) | -0.0 | -0.1 | 0.1 | 0.564 |

Percent Change of Total Body Fat and Intra-abdominal Fat Change by Average Weekly Duration of Exercise



* Significant difference compared with control group ($P<0.05$).

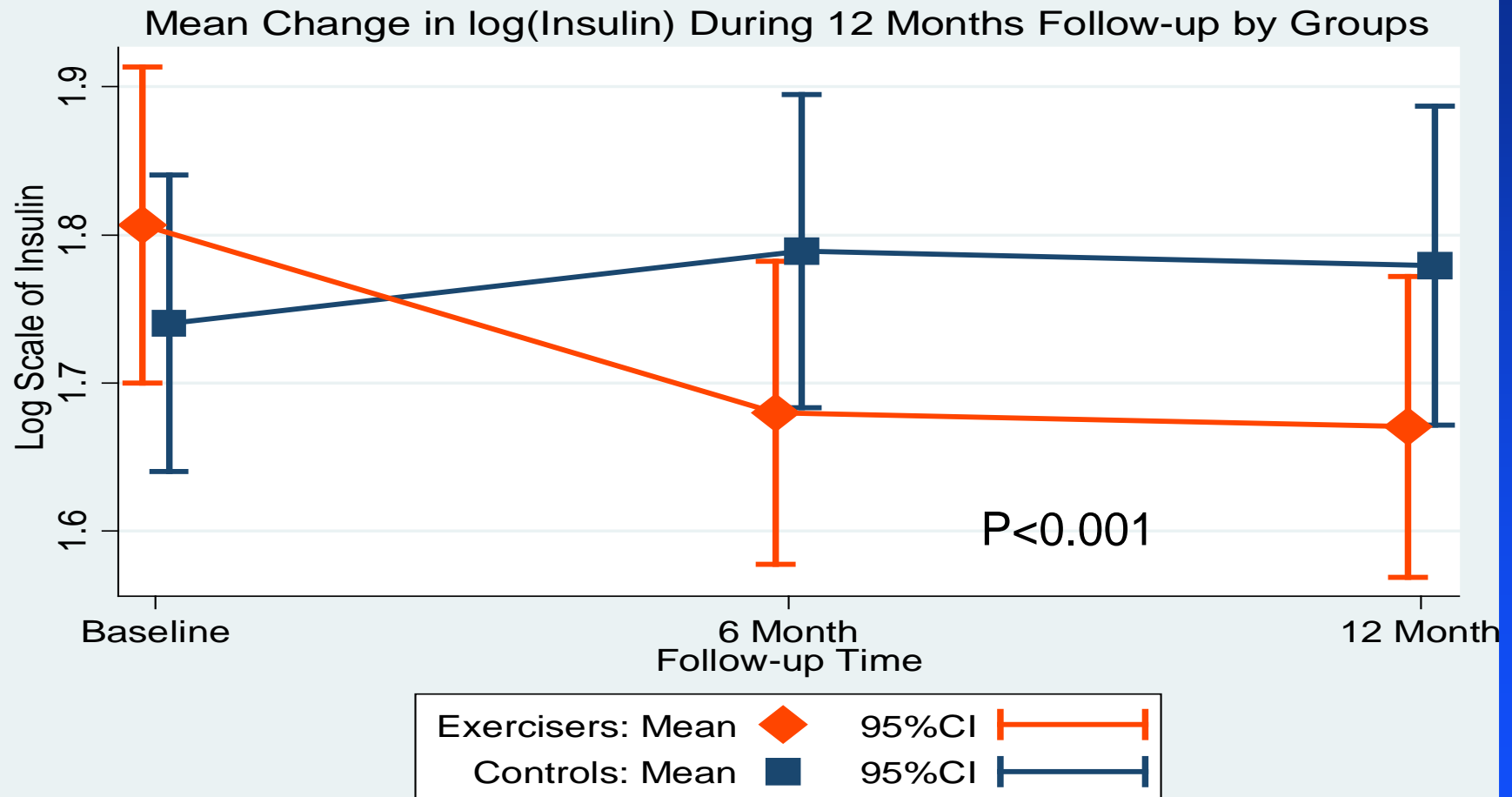
† Significant difference compared with low-active group ($P<0.05$).

Friedenreich et al., *Int J Obes* 2010;
35:427-35

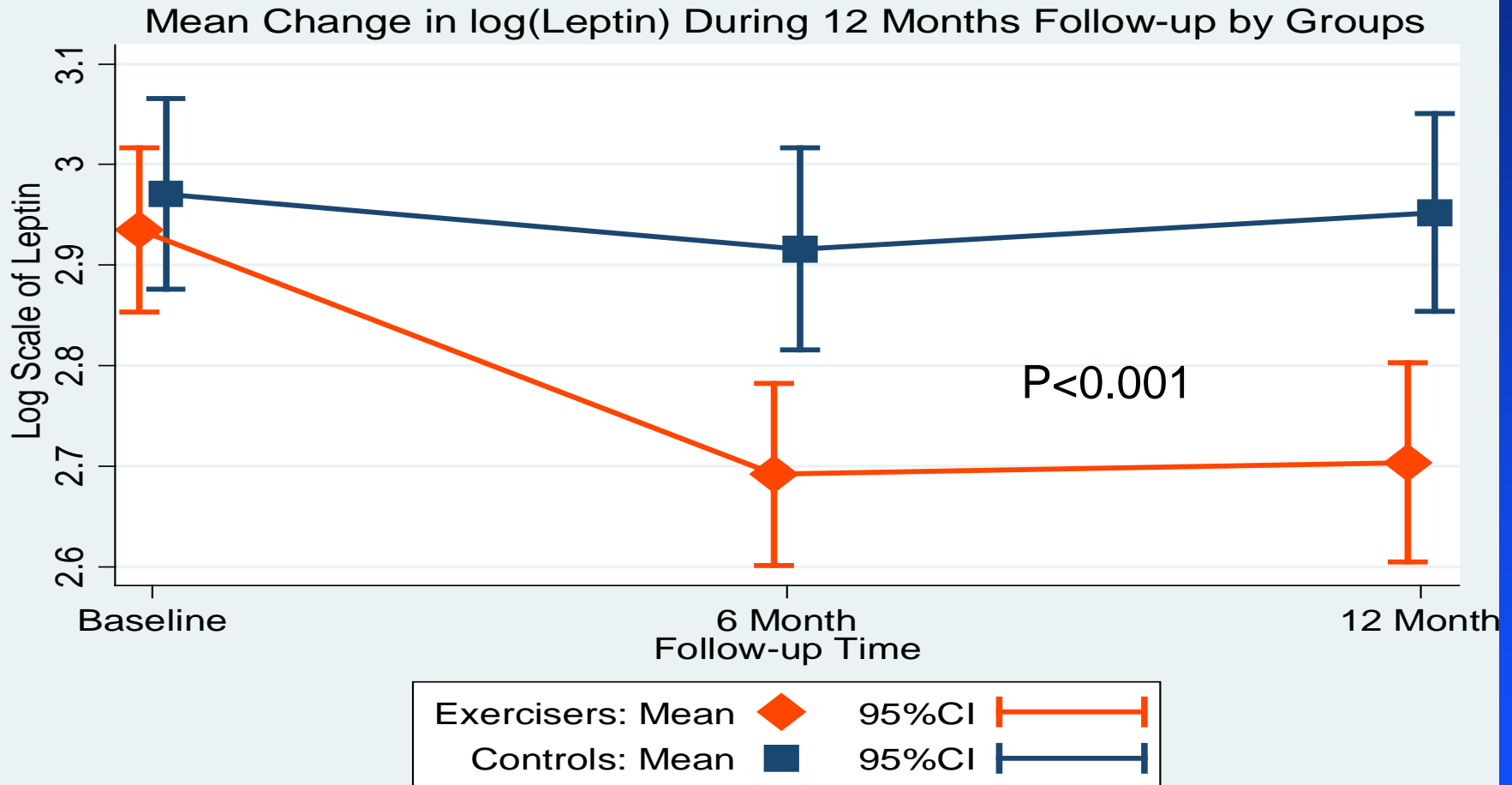
Insulin Resistance Outcomes

Friedenreich et al., Endocrine-
Related Cancer, 2011;18:357-69

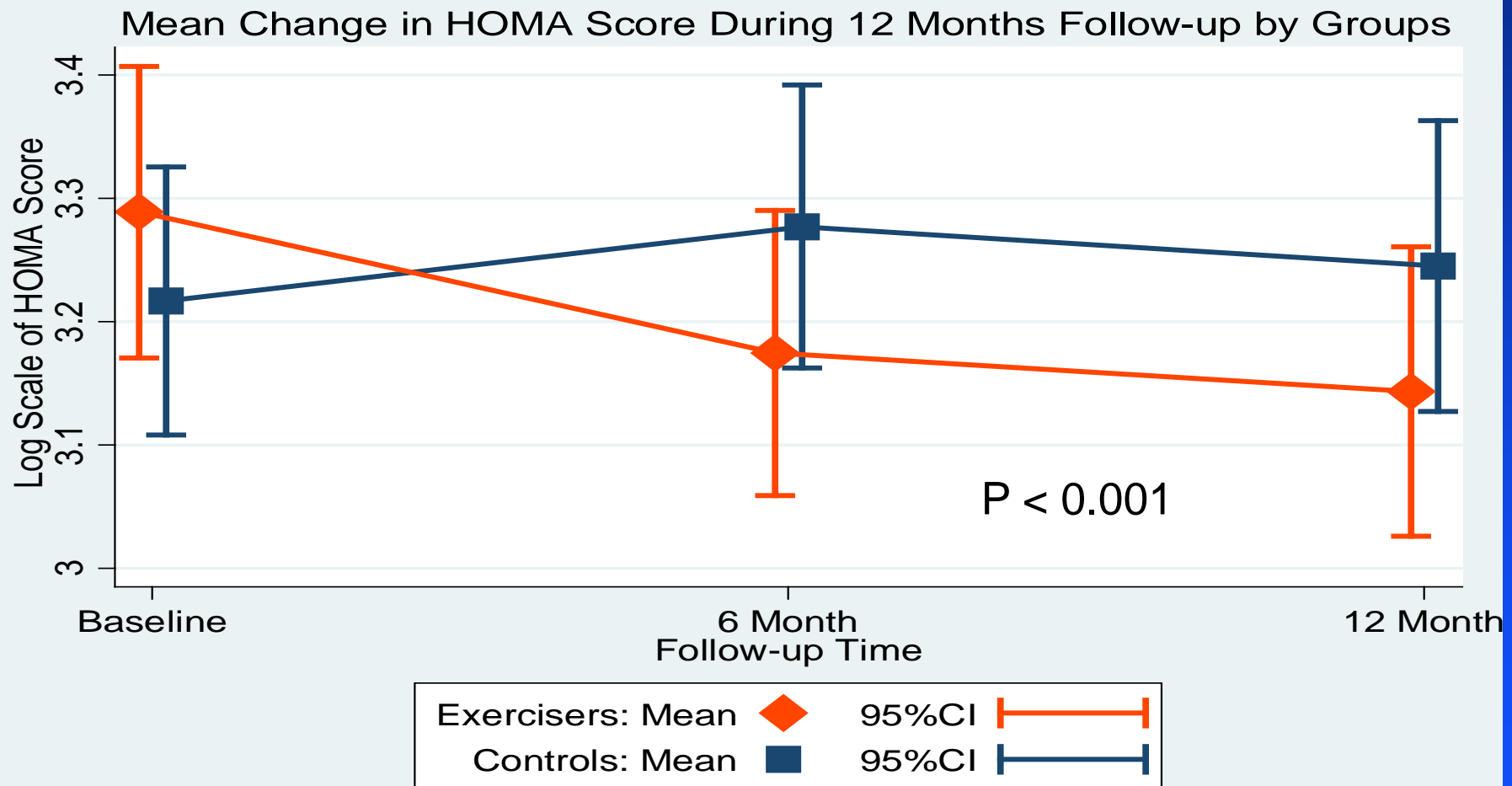
Impact of Exercise Intervention on Insulin



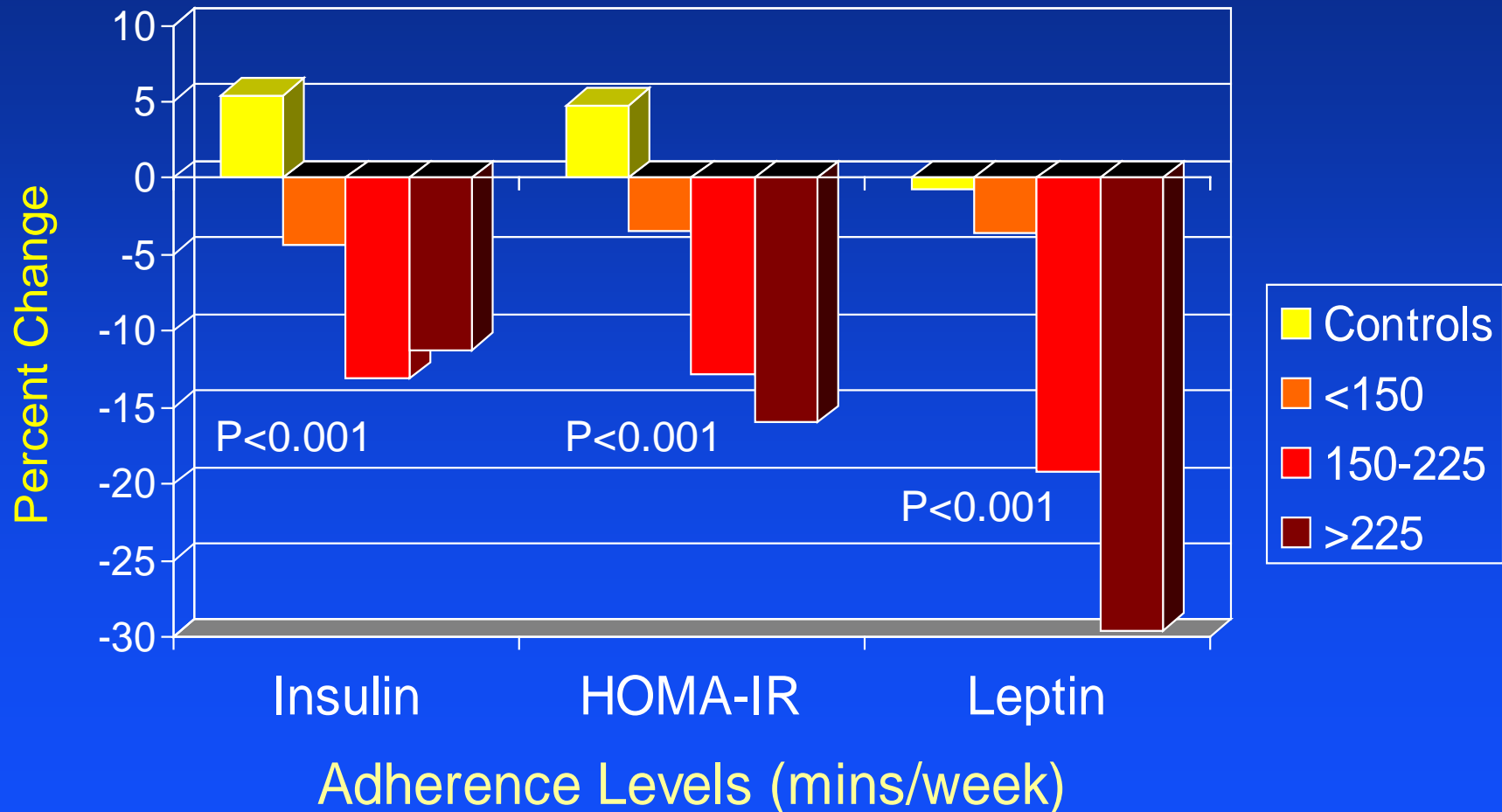
Impact of Exercise Intervention on Leptin



Impact of Exercise Intervention on Insulin Resistance (HOMA)



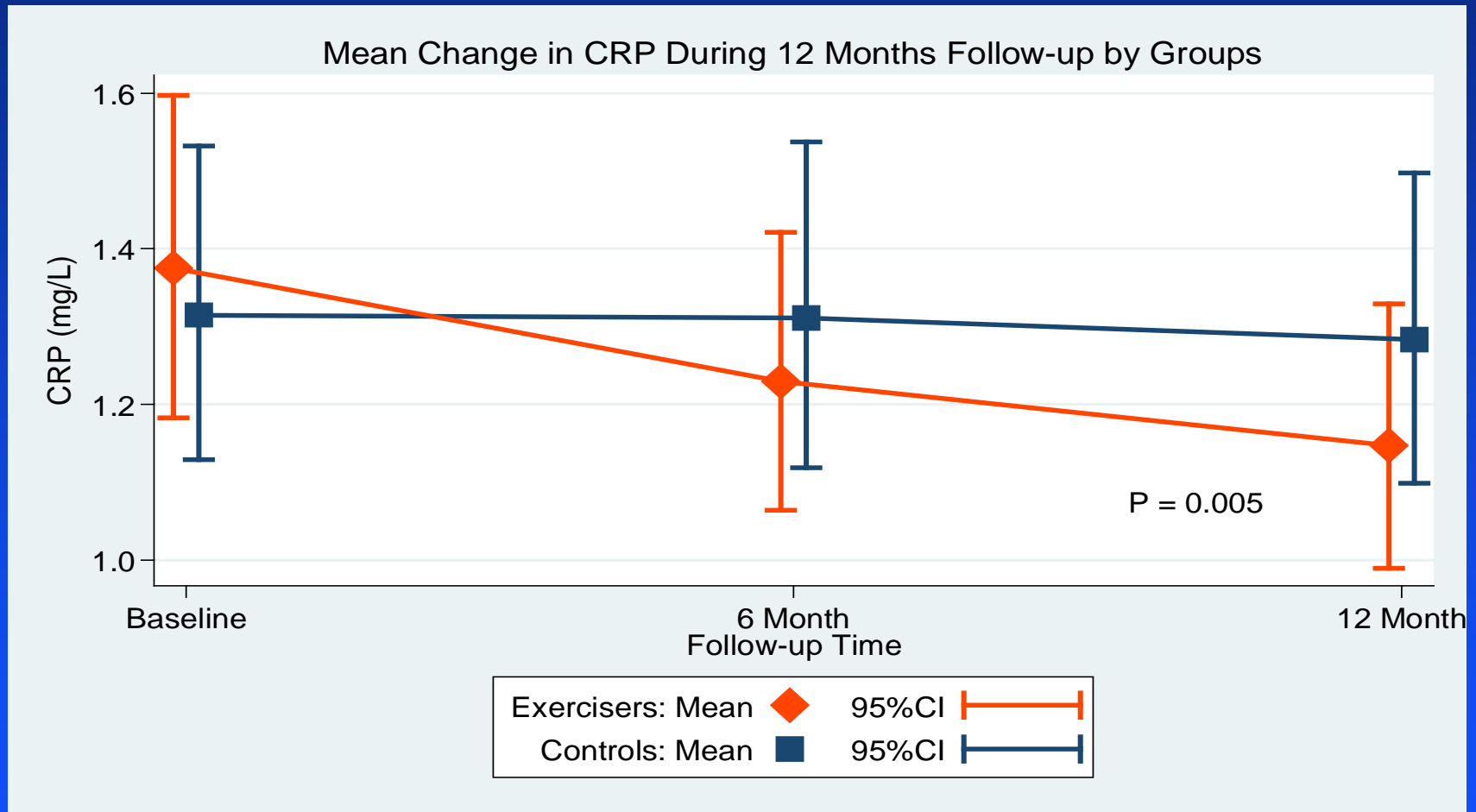
Percent Change in Insulin Biomarkers by Adherence Levels



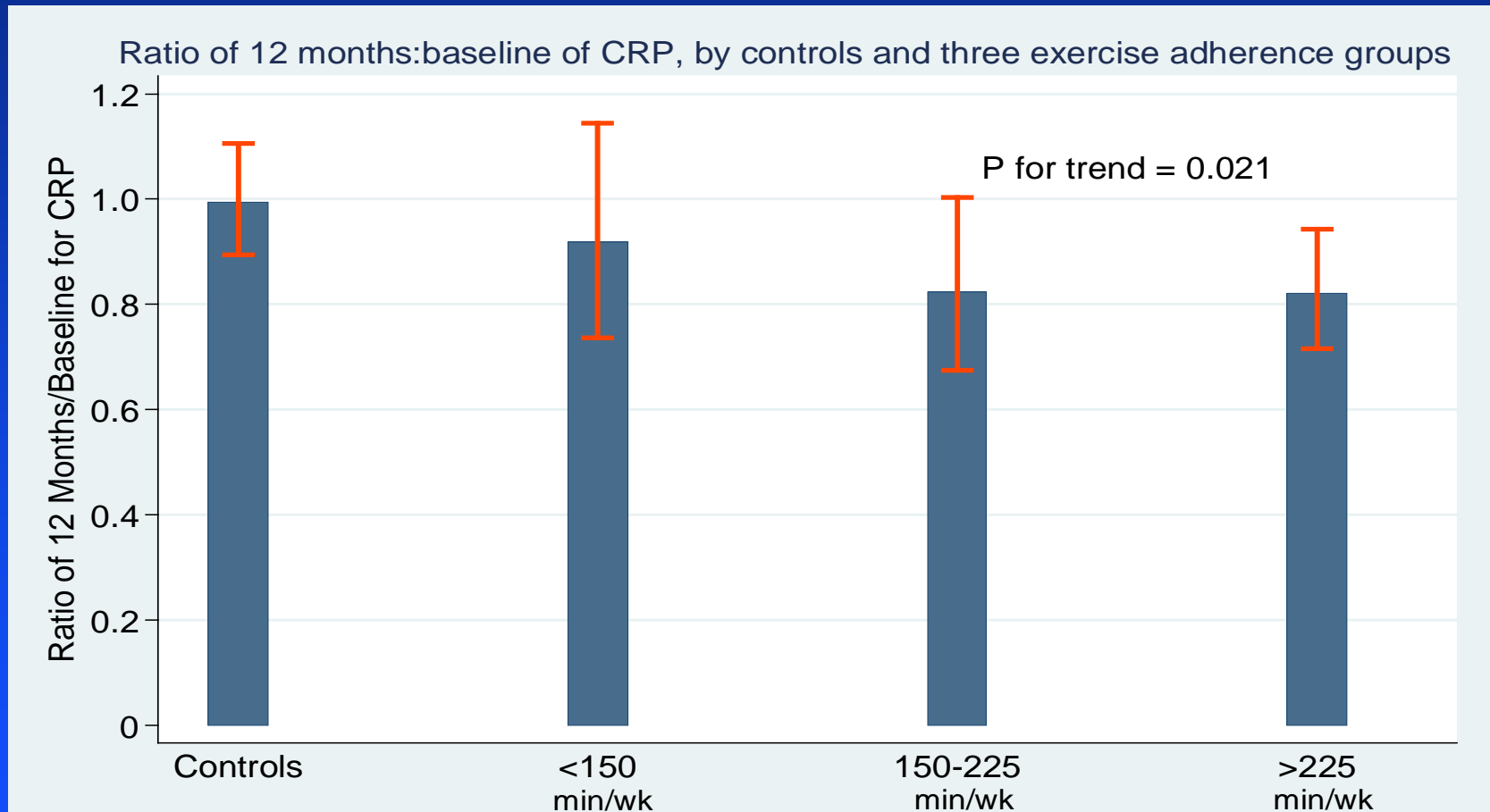
Inflammatory Marker Outcomes

Friedenreich et al., *Cancer Prev
Research* 2011;4 (epub)

Impact of Exercise Intervention on C-reactive Protein



Percent Change of C-reactive Protein by Average Weekly Duration of Exercise



Main Findings on Exercise and Breast Cancer Biomarkers

| Endpoint | PATH Trial | SHAPE Trial | ALPHA Trial |
|---------------------------|---|---|---|
| Sex hormones | ↓ estrone and estradiol restricted to women who lost >2% body fat | No effect on estrogens or androgens | ↓ estradiol and ↑ SHBG |
| Obesity | ↓ all adiposity measures | ↓ body fat but no effect on weight, BMI or hip circumference | ↓ all adiposity measures |
| Insulin resistance | ↓ insulin, leptin, HOMA score | Not reported | ↓ insulin, HOMA-IR, leptin, adiponectin/leptin ratio |
| Inflammation | ↓ C-reactive protein | Not reported | ↓ C-reactive protein |
| Publications | Irwin 2003; McTiernan 2004; Frank 2005; Campbell 2009 | Monninkhof 2009; Velthuis, 2009 | Friedenreich 2010a; Friedenreich 2010b, Friedenreich 2011 |



Funded by ACF and CCSRI

Breast Cancer and Exercise Trial in Alberta: Study Design

Recruit 400
postmenopausal healthy
women 50-74 years

Randomize

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

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

Compare high vs. moderate exercise groups on
**endogenous sex hormones, obesity and
inflammatory markers, insulin, glucose**

Follow-up at 24 months: examine exercise
maintenance and long term effect on biomarkers



Study Participants and Staff





**Alberta Moving Beyond Breast
Cancer (AMBER) Cohort Study**

Alberta Moving Beyond Breast Cancer Cohort (AMBER) Study

Study Time Line and Design

Courneya KS, Friedenreich CM (co-PIs), CIHR 2011-16

2012-2017

2017-2022

Enroll 1500 incident Stage I-IIIb breast cancer cases

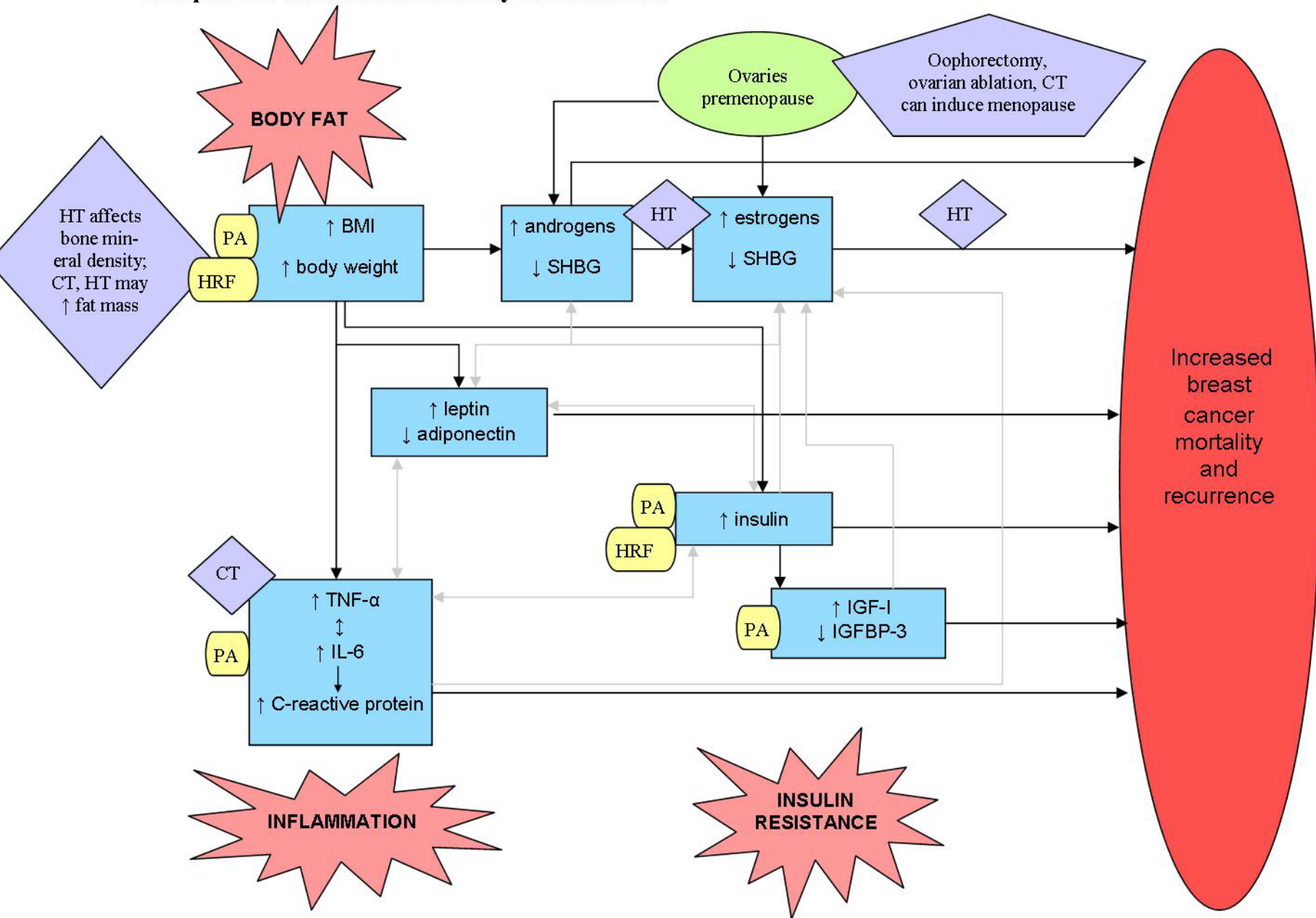
Measure physical activity, health-related fitness, determinants of PA, patient-related outcomes, biomarkers, lymphedema

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?

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

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

Figure 6. Hypothesized biologic model relating proposed biomarkers to long-term physical activity, health-related fitness, breast cancer therapies and breast cancer mortality and recurrence



CT- chemotherapy; HRF- health-related fitness; HT- hormone therapy; PA - physical activity

Lifestyle and Breast Cancer Risk: Current State of the Scientific Inquiry

- NCI Workshop on Feasibility of Physical Activity and Weight Control Trial to Prevent Breast Cancer, March, 2006
- **Background:**
 - ◆ Diabetes Prevention Program (DPP)
 - ◆ Dietary Approaches to Prevent Hypertension (DASH)
 - ◆ Look Action for Health in Diabetes (Look AHEAD)
- **Recommended study design:**
 - ◆ Primary endpoint: breast cancer
 - ◆ Inclusion criteria: age 45-75, postmenopausal, Gail score >1.7
 - ◆ Exclusion criteria: invasive breast cancer, DCIS, use of SERMs
 - ◆ Intervention: calorie-controlled diet and 150-225 mins/wk of moderate intensity activity, 5 days or more per week
 - ◆ Trial goal: 10% weight loss if BMI >25 kg/m², overall 5-7% avg wt loss
 - ◆ Sample size: Estimated breast cancer risk reduction with increased physical activity would be 18% and for weight control 12% with an additive effect with the two components for a 30% reduction in risk

Sample Size for RCT of PA and Weight Control for Primary Prevention of Breast Cancer

Table 4. Sample size estimations for a primary prevention trial of invasive and noninvasive breast cancer to evaluate physical activity and weight control

| Hazard ratio (control vs treatment 5-year disease-free interval rate) | Power, % | Minimum follow-up of 5 years | | Minimum follow-up of 3 years | |
|--|----------|------------------------------|-----------------|------------------------------|-----------------|
| | | Length of accrual, y | No. of patients | Length of accrual, y | No. of patients |
| 0.75 (97.8 vs 98.4) | 90 | 5.1 | 20 638 | 6.2 | 25 052 |
| | 85 | 4.5 | 18 262 | 5.6 | 22 468 |
| 0.80 (97.8 vs 98.3) | 80 | 4.1 | 16 350 | 5.1 | 20 442 |
| | 90 | 7.3 | 29 190 | 8.5 | 34 174 |
| | 85 | 6.5 | 25 974 | 7.6 | 30 774 |
| 0.85 (97.8 vs 98.1) | 80 | 5.8 | 23 472 | 7.0 | 28 108 |
| | 90 | 11.3 | 45 246 | 12.7 | 50 874 |
| | 85 | 10.1 | 40 502 | 11.4 | 45 976 |
| | 80 | 9.2 | 36 807 | 10.5 | 42 146 |

Ballard-Barbash et al. JNCI 2009;

- For a 20% risk reduction, power of 85-90% and 5 year follow-up would need 26,000-30,000 women
- No trial currently planned

Future Research Directions

- Investigate sedentary behaviour and light intensity activity as risk factors for cancers
- Improve PA measurements including objective assessments
- More precision on type, dose, timing of activity in relation to risk and survival
- Examine effect modification by other factors
- Conduct prospective observational studies of new biomarkers
- Need more mechanistic RCTs that evaluate different doses and types of PA
- Need more research on PA and survival at other cancer sites
- Ultimate objective: provide more quantitative data to enhance public health recommendations regarding PA type, dose, timing for cancer risk reduction and improved survival

Conclusion

- Strong, consistent evidence worldwide that PA reduces colon, breast, endometrial cancer risks and possibly also prostate, lung and ovarian cancers by 10-30% with a dose-response effect and some sub-group effects
 - ◆ Several plausible biologic mechanisms exist
 - ◆ RCTs are finding support for these mechanisms
- PA also improves survival after breast, colon and prostate cancers by 30% or more

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- ◆ Alberta Cancer Foundation
- ◆ CIHR
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- ◆ Dr Kerry Courneya, U of Alberta

- ◆ Others: Drs. Rollin Brant, Yutaka Yasui, Anne McTiernan, Rachel Ballard-Barbash, Tim Terry, Charlotte Jones, Melinda Irwin, Martin Yaffe, Norman Boyd, Frank Stanczyk, Robert Millikan, David Lau, John Mackey, Jeff Vallance, Nicole Culos-Reed, Margaret McNeely, Kristin Campbell, Kristina Karvinen

- Trainees: Dr. Christy Woolcott, Ame-Lia Tamburrini, Rita Biel, Dr. Brigid Lynch, Dr. Fabiola Aparicio-Ting, Dr. Shannon Conroy

- Staff: Department of Population Health Research, Alberta Health Services-Cancer Care