Exercise – evidence of a benefit and biological actions

Professor Robert Thomas

Bedford and Addenbrooke's Hospitals

Biological & Exercise Science
Coventry University

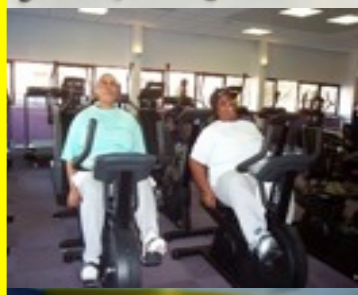
Coventry University

Bedford Hospital NHS
NHS Trust

Cambridge University Hospitals NHS
NHS Foundation Trust

- Evidence:
  - Improve well-being
  - Reduces relapse rates
- Underlying biological pathways?
- Potential risks?
- What's the optimum amount?
- When to start?





Meta analysis of 33 RCT studying exercise interventions after cancer

- Fatigue and tiredness
- Mood, anxiety & depression
- Muscle power
- Exercise capacity
- Distance walked in 5 minutes
- Overall Quality of life

Fong J, Hong Kong & Liam Bourke L, Barts *BMJ* 2012; 344:

BMJ

Comprehensive review of 85 RCT exercise interventions after cancer:

- Exercise was safe
- Aerobic fitness, strength and flexibility
- Anxiety and depression
- Self esteem
- Fear of relapse
- Fatigue
- Body image size and composition
- Overall quality of life

Schmitz KH et al (2010) Med Sci Sports Exerc 42: 1409-26

AMERICAN COLLEGE of SPORTS MEDICINE

Androgen Deprivation Therapy

Androgen deprivation therapy

121 men with Ca P starting ADT
Resistance and aerobic exercise programme

Significant improvement in:

- Muscle strength
- BMI
- Abdominal fat, triglycerides, blood sugar (Metabolic syndrome)

Segal et al JCO, Vol 27, No 3 , 2009: pp. 344-351

Prostate cancer guidelines 2014

National Institute for
Health and Clinical Excellence

Cancer Related Fatigue

Cancer Related Fatigue

- 28 RCT and 2 meta analysis reduces the severity of fatigue

- Supervised aerobic exercise programmes more effective.

- Cramp et al Cochrane Database Syst Rev 2008
- Velthuis et al Clin Oncol 2010

Why supervised programmes

- Social interaction
- Improves safety
- Motivation to turn up and do more
- Dietary advice
- Excess or wrong type of exercise

Level 4 qualification in cancer exercise rehab

- The Wright Foundation
- Can rehab

- Motivational interviewing
- Sensitive to needs and ongoing toxicities
- Appropriate exercise:
  - O_2 debt creates post-exertional malaise (>50% Vo_2max).
  - Surrogate AT is ~60% of max HR (Max HR is 220 – age).

Wilmore JH (2005) Physiology of Sport & Exercise

WE ARE MACMILLAN. CANCER SUPPORT

Cambridge University Hospitals NHS Foundation Trust

The ROYAL MARSDEN NHS Foundation Trust

440 men with prostate cancer treated over 10 years

Toxicity

- Vaizey rectal toxicity score
- NCI common toxicity score
  - Rectal bleeding
  - Erectile function
  - Urinary incontinence

Lifestyle

- Smoking habits
- BMI, age
- General practice physical activity questionnaire

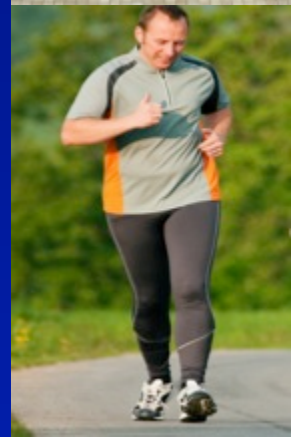
WE ARE MACMILLAN. CANCER SUPPORT

Cambridge University Hospitals NHS
NHS Foundation Trust

The ROYAL MARSDEN
NHS Foundation Trust

440 men with prostate cancer treated with RXT correlated vaizey and NCI toxicity scores with lifestyle habits

	Exercise	Smokers	Age	BMI
Rectal toxicity	P<0.05	P<0.05	**NS**	P<0.05
Incontinence	P<0.05	P<0.05	**NS**	**NS**
Erectile function	P<0.05	**NS**	**NS**	**NS**



Thomas, *Clinical Oncology* 2013

Obesity and breast cancer outcomes

- Systematic review of 43 studies
- 33% higher risk for both breast cancer–specific death and death from all causes comparing obese with lean women

Protani. *(2010) Breast Cancer Res Treat* ***123****:627.*

Weight reduction

Women's Intervention Nutrition Study (WINS)

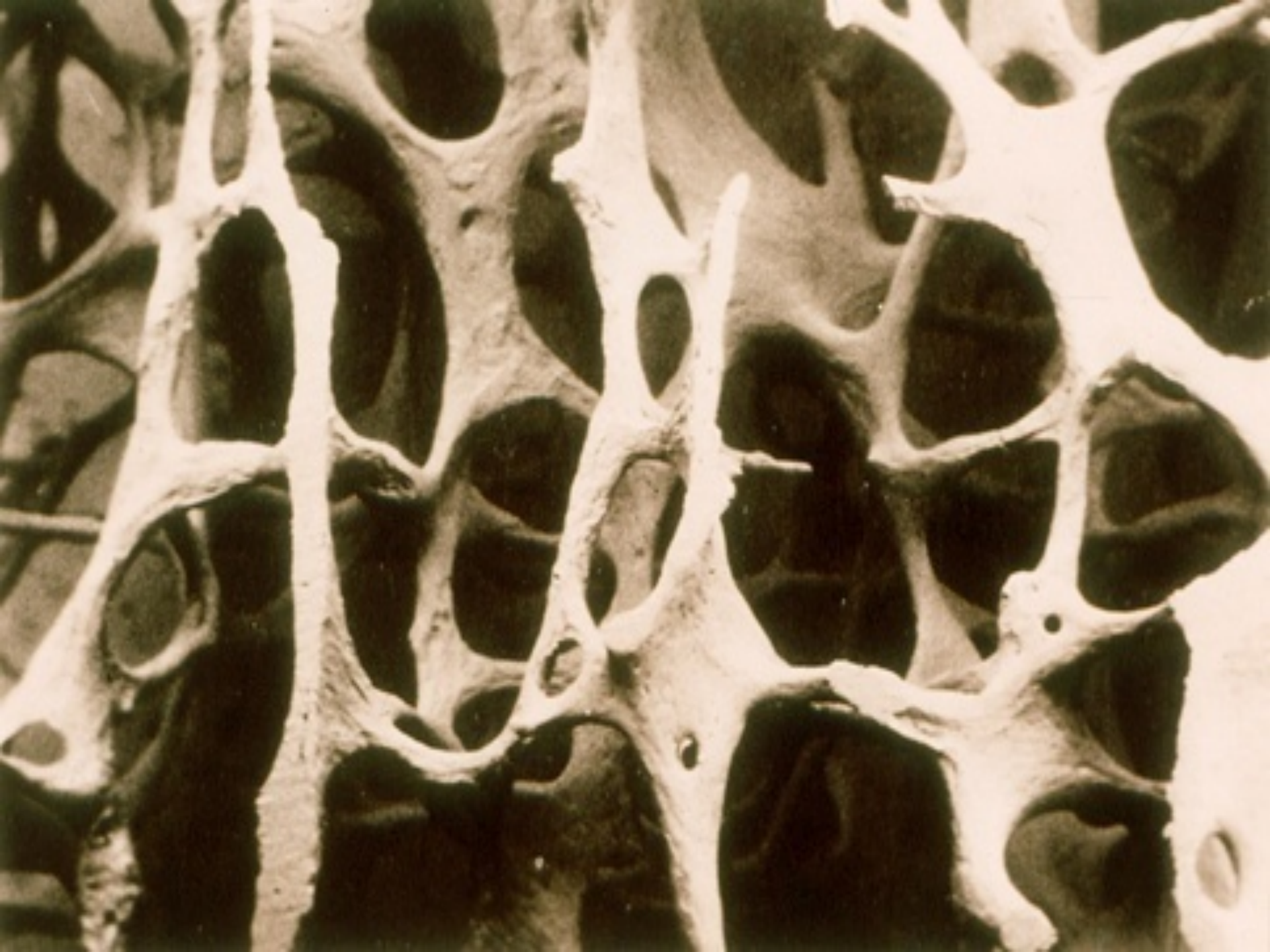
- Eight bi-weekly counselling sessions at 60 months
- Dietary fat intake weight and exercise improved

Chlebowski RT, et al, JCO 2005

Enhance Recovery Good Health for You (ENERGY)

- Supervised exercise and dietary intervention programme
- Significant weight reduction at one year

Rock CL et al, JCO 2015

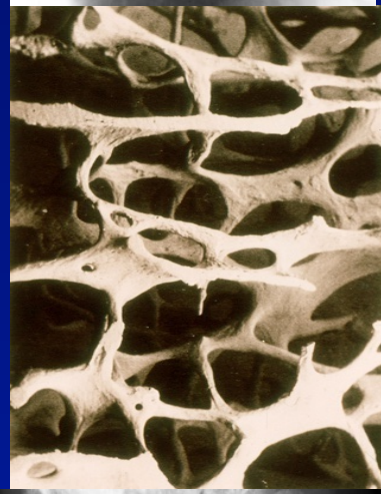


Exercise for bone health

RCT of 223 women breast cancer taking risedronate, calcium & vit D:

- Usual care v 30mins 4-7 times/wk aerobic
- BMD baseline and 6 months
- If adherence >50% in exercise programme
  - 20% (Significantly) different BMD

Waltman et al. (2009)



1. Calcium intake and bone mineral density: systematic review and meta-analysis:

- 59 RCT
- No clinical benefit from calcium and vit D supplements

Vicky Tai BMJ 2015;351:h4183

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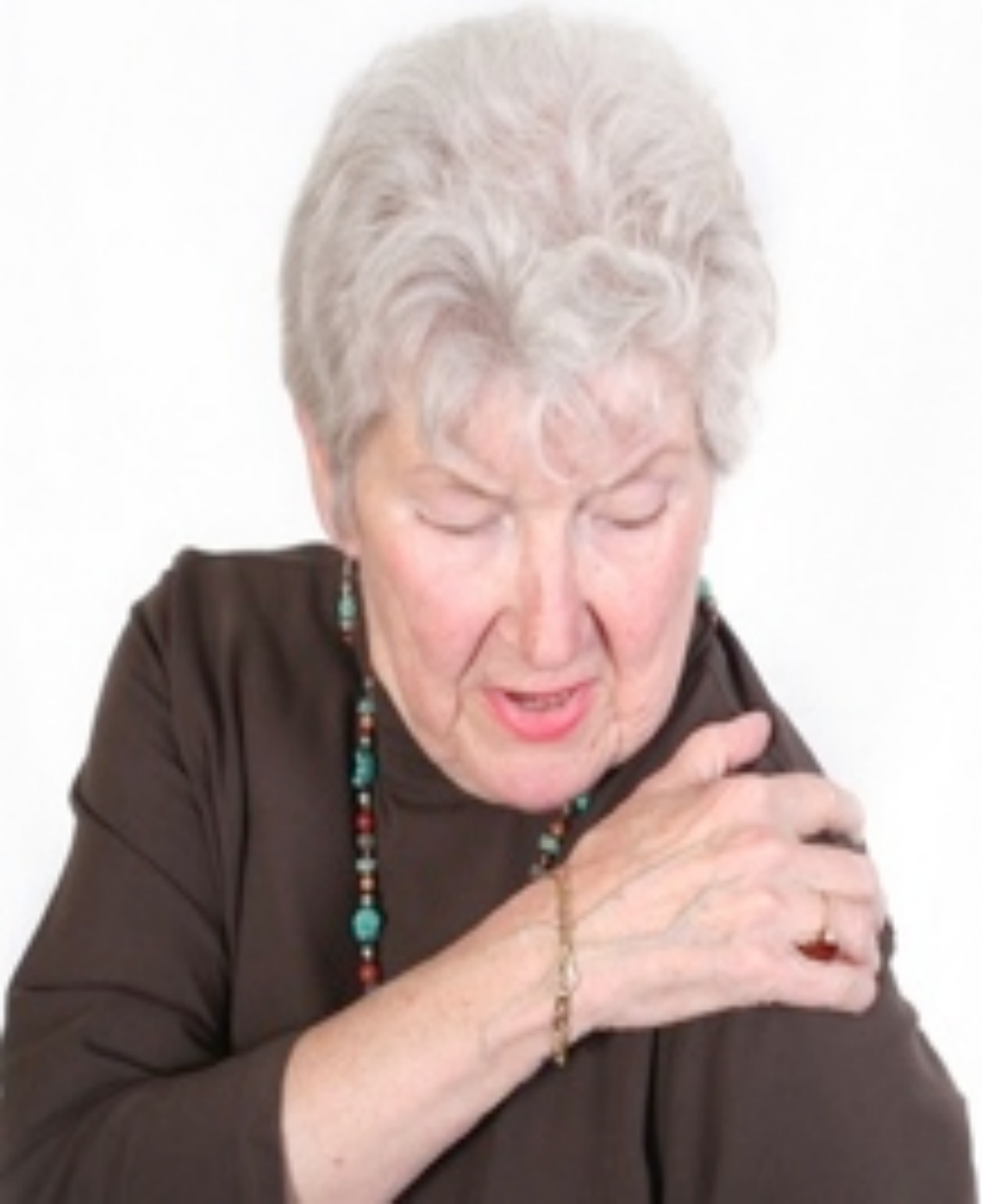
2. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

- 15 RCT 8151 participants
- Increase cardiovascular risk

Bollard et al B*MJ* 2010;341:c3691



Arthralgia incidence

55% of breast cancer*

40% prostate cancer survivors*

- Osteoarthritis
- Chemotherapy (Taxotere)
- Tamoxifen
- Aromatase inhibitors
- Herceptin and other biologicals

* Younger age

RCT of an exercise intervention for aromatase inhibitor induced arthralgia (HOPE study)

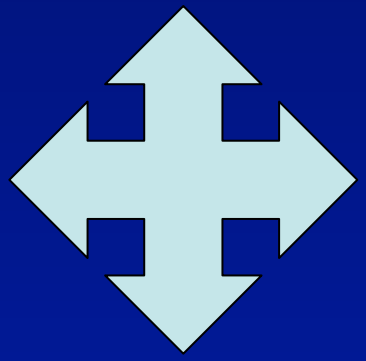
121 women with breast cancer taking an AI

12 weeks exercise intervention programme:

- Reduced arthralgia
- Improve QoI
- Dose-response relationship

Irwin et al JCO 2015,(33),10.

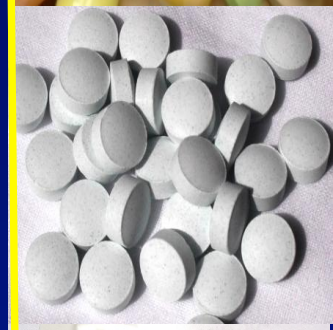
Barrier to exercise is arthralgia



Yang NCRI 2015

Over the counter supplement usage in UK

- General population 30%
- Cancer population 55%
- Arthritis & cancer population 65%



- Bauer et al. Integr Can Ther. 2012 11(2):83.
- Uzzo et al. BJU Int. 2004. 93(7):955-60
- Bishop et al Journal of Health Psychology 2007; 12:851–67.

Arthritis Research UK

A report by Arthritis Research UK
Complementary and alternative medicines

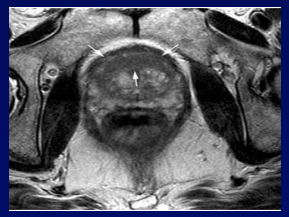
Complementary and alternative medicines for the treatment of rheumatoid arthritis, osteoarthritis and fibromyalgia.

Systemic review OTC supplements and arthritis

- Fish oils
- Chondroitin
- Glucosamine
- Polyphenol rich whole foods
  - Turmeric
  - Pomegranate
  - Green tea
  - Broccoli
  - Rosehip
  - Mushrooms

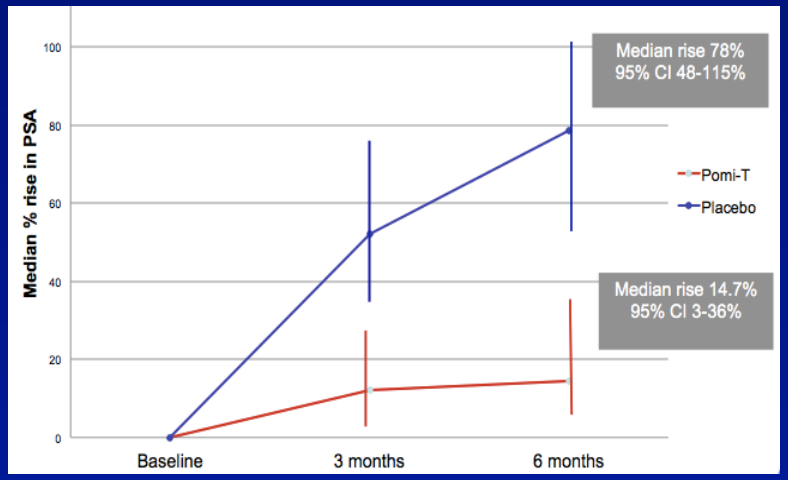
NHS National Institute for Health Research

NCRN

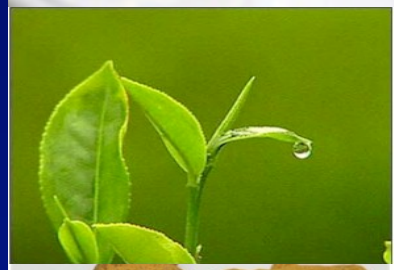


Prostate Action

Complementary therapy and lifestyle clinical trials committee



Double-blind, placebo RCT evaluating a polyphenol-rich food capsule in men with prostate cancer - The Pomi-T study Thomas et al 2014



Potential anti-arthritis mechanism of phytochemicals within Pomi-t

1. Anti-oxidant properties, which protect the joint from oxidative damage [Giovannucci et al., 2006; Stivala 2000].

2. Anti-inflammatory properties, which reduce the discomfort and stiffness [Mitchel PG]

3. Anti-apoptopic effects on chondrocytes reducing cartilage degeneration [Shen].

4. Modulation metalloproteinases - remodeling and the destruction of cartilage in arthritic joints. [Dahlberg, Brinckerhoff].

A double blind RCT of a phytochemical rich supplement for hormonal induced arthralgia (EudraCT 2015-002018-66)

210 participant with arthralgia on Hormone therapies

110 randomised placebo

110 randomised to interventional supplement

Arthralgia scores
Exercise levels
QoL
Hot flushes
Breast pain

Arthralgia scores
Exercise levels
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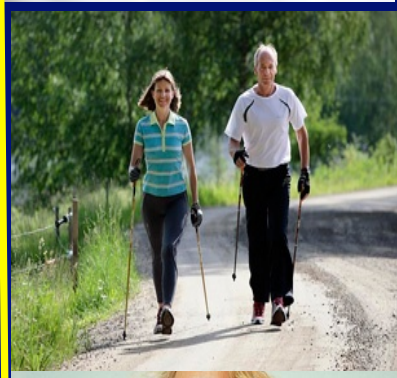


Improved outcomes

Exercise after breast cancer

- 933 BC survivors PE> 2.5 hrs/week 67% reduction in RR
  Irwin M et al 2007 JCO
- 4482 BC survivors PE > 2.8 hrs/wk 35-49% reduction in RR
  Holick C et al 2008
- 1879 women, The LACE study OS better upper versus lower quarter
  Sternfeld et al (2009)
- 2987 women Nurses Health study 3-5 hrs/wk better OS and RR
  Holmes et al JAMA 2005
- 1490 BC 30 mins 6 days a wk (+ >5 fruit/veg a day) greater survival
  Pierce et al 2007JCO
- 4826 women, The Shanghai Cancer Registry; 8 MET/wk v sedentary
  Chen et al 2001

Exercise after bowel cancer

Melbourne Collaborative cohort study, 526 patients with ca colon. At 5 years:

- 57% alive (non-exercisers) v 71% alive (1-2 sports/wk)

Haydon 2006

Intergroup CALGB 89803 study, stage III:

- 35% overall survival difference upper to lower quartiles of activity

Meyerhardt 2005;

Health Professional study (USA)

- Lower cancer specific mortality >27 v < 3 METS per week

Meyerhardt 2009

NIH–AARP Diet and Health Study

- 31% overall survival LTPA ≥7 h/wk (TV watching linked with mortality)

Arem JCO 2014

Exercise after Prostate cancer

- Health Professionals Follow-Up Study (2705). Physical Activity and Survival after Prostate Cancer.

  Kenfield *et al. JCO 2011*

- Physical Activity and Risk of Prostate Cancer Progression: Prostate Strategic Urologic Research Endeavour.

  Richman et al. *Can Res 2011*

- Health professional study – fatal prostate cancers lower in men who exercised over the age of 65 years

  Giovannucci et al Arch Intern Med. 2005

The National Cancer Institute

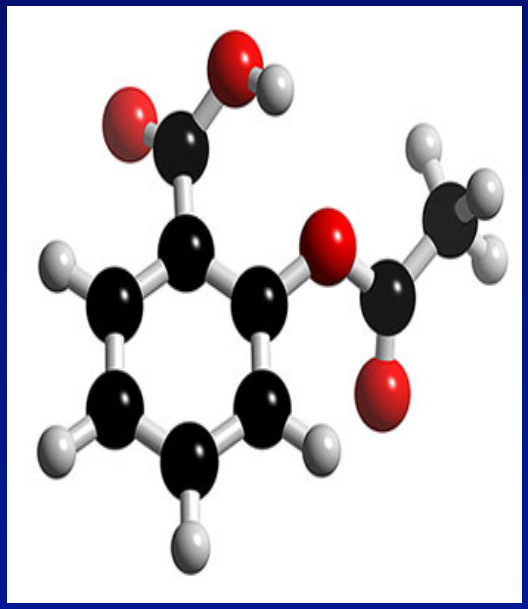
- Systemic review
- 45 observational studies:

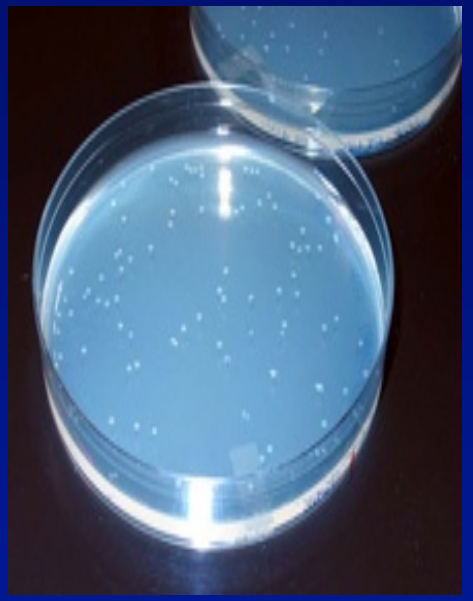
2-3 hours of moderate PA a week is linked to a >30% reduction in relapse

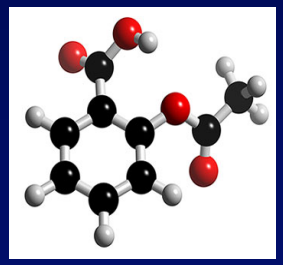
Ballard-Barbash et al Nat Can Inst 2012

No study has reported higher PA with worse outcomes

Anti-cancer biology







Insulin Like Growth Factor

Exercisers lower IGF-1 higher IGFBP3

Kaaks et al 2002

Effects proliferation, angiogenesis, inhibits apoptosis

[Yu 2000, Freier 1999]

Colorectal cancer lower IGF linked to 48% RR

Haydon 2006

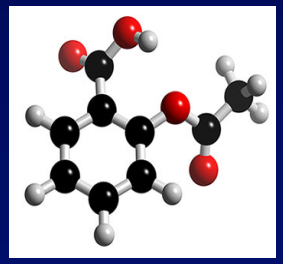
Breast cancer IGF linked to PA levels and survival

Irwin 2009

Prostaglandins

- Prostaglandins (PGE_2) made from arachidonic acid via COX-2
- COX-2 is induced by cytokines, tumour promoters
- Cancer progression, apoptosis, invasion, angiogenesis and metastasis
- Study involving rectal biopsies - increase in PA from 5.2 to 27.7 MET-hrs /wk 28% < mucosal PGE_2

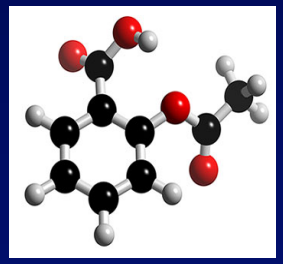
Martinez et al 1999.



Vasoactive Intestinal Protein

- Proliferative and pro-metastatic properties
- Sedentary patient's have higher VIP titres
- Exercise increases anti-VIP antibodies

Velijkovic et al 2012.



Oestrogen levels

Proliferative effect breast uterine ovarian cancers

Kaaks 2002

Exercise lowers wt then oestrogen in post-men women

Friedenreich 2010

Oestradiol lower amoung exercisers weight loss adjusted

Friedenreich et al 2009

Every 100 min of exercise linked with 3.6 % lower oestrogen

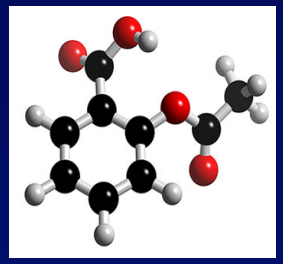
Schmitz 2015

Epigenetics

180 genes were expressed more favourably men who jogged, played tennis or swam for > 3 hrs/wk, compared with sedentary men. Kenfield 2011

BRCA1 and BRCA2 Magbanua 2012

P53 Sharafi 2012



Leptin

- Neuropeptide cytokine cancer promoting properties

  Hoffmann-Goetz 1998

- Made in fat cells - overweight people - higher levels

  Surmacz 2007

- 60 mins exercise directly reduces leptin levels

  Kraemer 2002

Irisin

A type I transmembrane messenger protein, produced in muscle cells in response to exercise

Reduces proliferation, migration in malignant cells lines but not benign cells. BostrÖm 2012.

Enhanced the cytotoxic effect of doxorubicin in malignant cells not benign cells Gannon 2015

Some criticism of the ELISA kit assay mass spectrometry found a significant difference Jedrychowski 2015.

Indirect effects

Risks

Potential dangers

- Pelvic symptoms
- Heat shock proteins
- Free radicals
- Testosterone

Heat Shock Proteins

Increased after stress to body:

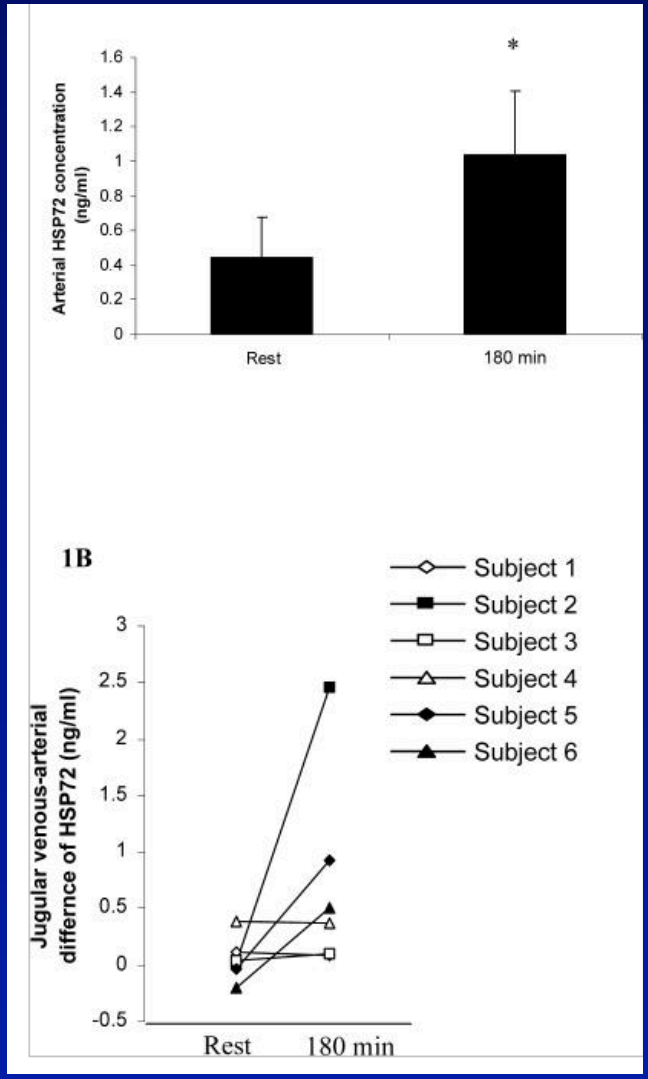
- Myocardial infarction
- Infection
- Hyperthermia
- Dexamethasone
- Chemotherapy
- Exercise

Protects stressed cells - blocks apoptosis

Protects normal tissues

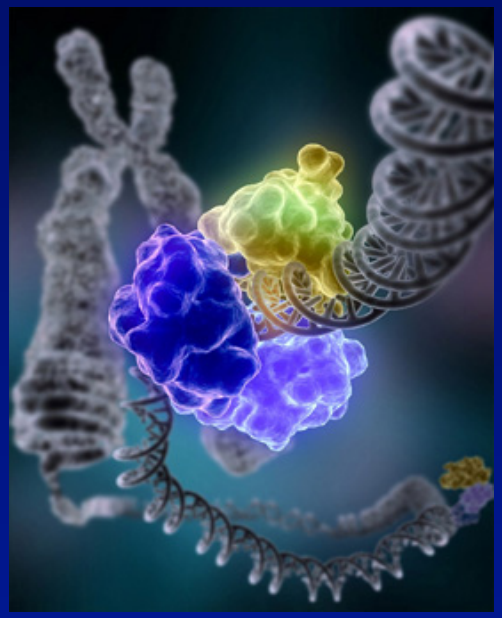
Generated by cancers themselves

Exercises increases effectiveness of adriamycin



Fehrenbach E Exerc Immunol Rev 2001;7:66-89.

Free radical formation



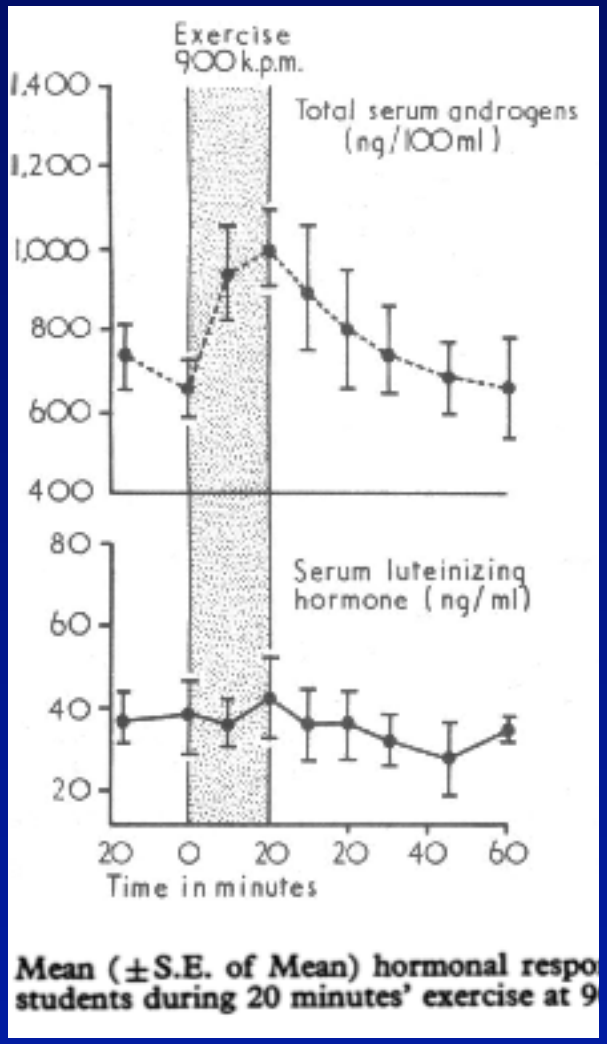
- Transient increase in ROS
- Adaptive process
- Increases antioxidant enzymes:
- SOD, glutathione and catalase
- Long term antioxidant.

Gomez-Cabrera. Free Radic Biol Med 2008 15;44(2):126-31.

Ji LL et al Ann NY Acad Sci. 2001; 928:236-47.2001

Kojda G et al. Cardiovascular research. 2005;67:187–97.

Testosterone



Mean (±S.E. of Mean) hormonal respo
students during 20 minutes' exercise at 9

- Short lived
- Total not free testosterone increases
- This effect not seen in over 55 years
- Levels fall with regular training

Kaaks. *Ann NY Acad Sci* 2002; 963: 268-281.
Hayes Aging Male 2015, 18(3):195-200
Sutton BMJ 1973, 1, 520-22
Safarinejad Endocrinol 2009 ;200(3):259-71
Craig Mech Ageing Dev. 1989 49(2):159-69.

At one year PSA was lower in men who exercised and ate well compared to other group

PSA

Control - increase by an average of 6%

10% difference significant at P>0.01

Intervention - decrease by average 4%

Trial entry

At one year

Ornish D, et al 2005.

How much exercises?

What level of exercise is required?
Prostate

Cancer of prostate Strategic Urology Research Endeavour 2011

1,455 men who had been diagnosed with early-stage prostate cancer

This trial showed that walking at a pace of at least 3 miles/hr for 3 hours or more per week , had 57% less likely to develop PSA relapse but not those walking < 3m/hr had little benefit

Richman E et al Cancer Res 2011

What level of exercise
Breast cancer relapse

Dose–response analysis:

2 % reduction of risk per 25 MET-h/week

5 % benefit for each 35 MET-h/week

- eq. 4 h walking 2 m/h, 1 h running 6 miles/h

5 % extra benefit or each extra 2 h/week increment in moderate plus vigorous recreational activity

Wu Y et al 2013. Breast Can Research and Treatments 137 (3)869-882

PACES RCT during chemotherapy

- 230 women receiving chemotherapy
- Supervised High intensity v Home based v standard
- HI & HB >standard but HI > HB:
- Less decline in cardiorespiratory fitness ($P < .001$),
- Better physical functioning ($P \leq .001$),
- Less nausea and vomiting ($P = .029$)
- Less pain ($P = .003$),
- Better muscle strength ($P = .002$)
- Less fatigue ($P < .001$)

Van Waart JCO 2015

When to start?

Pre-habilitation

- **Systematic review and meta-analysis**
- 4597 citations in 21 studies
  - Postoperative pain,
  - Length of stay
  - Physical function

Mina S Physiotherapy. 2014

PACES RCT during chemotherapy

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Van Waart JCO 2015

Conclusion

- Strong evidence for wellbeing
- Reasonable evidence for outcomes
- Feasible biological mechanisms of action
- Start early aim for 3-5 hours / week
- Safe
- Role for linked targeted nutritional strategies
- We need to try harder to motivate patients

More information

cancernet.co.uk

Talk: www.cancernet.co.uk/exercise.htm

Thomas & Holmes. BJMP 2014
Davis & Thomas BJC 2011

Robert Thomas

@cancernetuk

Monthly lifestyle news updates

Safarinejad MR The effects of intensive, long-term treadmill : a randomized controlled study. J Endocrinol 2009 ; 200(3):259-71

Craig BW et al Effects of progressive resistance training on growth hormone and testosterone levels in young and elderly subjects. Mech Ageing Dev. 1989 49(2):159-69.

Sgro P et al Testosterone responses to standardized short-term sub-maximal 30 mins. GH and testosterone transient rise J Endocrine Invest 2014 37(1):13-24

Hackney AC et al Endurance exercise training and reproductive endocrine dysfunction in men: alterations in the hypothalamic-pituitary-testicular axis. Curr Pharm Des 20017(4):261-73.

Enea C et al Effects of menstrual cycle, oral contraception, and training on exercise-induced changes in circulating DHEA-sulphate and testosterone in young women. Eur J Appl Physiol 2009;106(3):365-73

Niklas BJ et al Testosterone, growth hormone and IGF-I responses to acute and chronic resistive exercise in men aged 55-70 yrs. Int J Sports Med 1995 16(7):445-50.

Kaaks R, Lukanova A; Effects of weight control and physical activity in cancer prevention: role of endogenous hormone metabolism. *Ann NY Acad Sci* 2002; **963**: 268-281.

Irwin ML, Alvarez-Reeves M, Cadmus L, Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. Obesity. 2009 17(8):1534-41.

Haydon AM, McInnis RJ, English DR, *et al.*; The effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* 2006; **55(1)**: 62-67.

Friedenreich CM, Woolcott CG, McTiernan A *et al*; Alberta physical activity and postmenopausal breast cancer prevention trial: Sex hormone changes. *J Clin Oncol* 2010; 28(9): 1458-66.

Schmitz KH, et al 2015 Dose–response effects of aerobic exercise on estrogen among women at high risk for breast cancer: a randomized controlled trial

Surmacz E; Obesity hormone leptin; a new target for breast cancer? *Breast Cancer Res* 2007; **9(1)**: 301.

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Kraemer RR et al Leptin levels reduce after exercise. Exp Biol Med 2002; 227(9):701-0

Kaaks R, Lukanova A; Effects of weight control and physical activity in cancer prevention: *Ann NY Acad Sci* 2002; **963**: 268-281.

Hayes LD Six weeks of conditioning exercise increases total, but not free testosterone in lifelong sedentary aging men. Aging Male 2015, 18(3):195-200

Sutton JR et al Androgen response during physical exercise BMJ 1973, 1, 520-22

Xie Y et al Vasoactive intestinal peptide transactivates the androgen receptor through a protein kinase A-dependent extracellular signal-regulated kinase pathway. Mol Pharmacol. 2007; 72(1): 73-85.

Valdehita A et al. Nuclear localization of vasoactive intestinal peptide (VIP) receptors in human breast cancer. Peptides 2010; 31(11):2035-45

Ciocca DR Heat shock proteins in cancer: diagnostic, prognostic, predictive, and treatment implications Cell Stress Chaperones. 2005; 10(2): 86–103.

Hahleh Z et al Heat shock proteins in cancer: targeting the 'chaperones'. Future Med Chem 2012;4(7):927-35

Kavazis AN, Smuder AJ, Min K, et al. Short-term exercise training protects against doxorubicin induced cardiac mitochondrial damage independent of HSP72. Am J Physiol. 2010:299.

Powers SK, Locke, Demirel HA. Exercise, heat shock proteins, and myocardial protection from I-R injury. Med Sci Sports Exerc. 2001;33:386–392.

Lanchaster GI Exercise induces the release of heat shock protein 72 from the human brain in vivo Stress Chaperones. 2004 9(3): 276–280.

Fehrenbach E and Northoff H. Free radicals, exercise, apoptosis, and heat shock proteins. Exerc Immunol Rev 2001;7:66-89.

Fehrenbach E and Northoff H. Free radicals, exercise, apoptosis, and heat shock proteins. Exerc Immunol Rev 2001;7:66-89.

Gomez-Cabrera MC et al. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radic Biol Med 2008 15;44(2):126-31.

Ji LL et al Exercise at old age: does it increase or alleviate oxidative stress? Ann NY Acad Sci. 2001; 928:236-47.2001

Gomez-Cabrera MC et al. Oxidative stress in marathon runners: interest of antioxidant supplementation. Br J Nutr 2006 (96) Suppl 1:S31-3.

Kojda G et al. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? Cardiovascular research. 2005;67:187–97.

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Freier S, Weiss O, Eran M, et al.; Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. *Gut* 1999; **44**: 704-708.

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