

# Tamas Hickish

Consultant Medical Oncologist  
Poole and Bournemouth Hospitals  
Visiting Professor Bournemouth  
University

# It is getting better...

- Death rates for cancer are falling in all developed countries
- England and Wales - rate of improvement exceeds others
- Data indicates E and W very 'efficient'

» Pritchard and Hickish 2008

# Meta-analysis of Ovarian Suppression as Adjuvant Therapy for Breast Cancer

|   | Recurrence                 | Death after recurrence     | All deaths                 |
|---|----------------------------|----------------------------|----------------------------|
| <b>Univariate models</b>  |                            |                            |                            |
| Age (continuous, years)   | 0.96 (0.95-0.96), p<0.0001 | 0.95 (0.94-0.96), p<0.0001 | 0.96 (0.95-0.96), p<0.0001 |
| Age ≤40 years   | 1.62 (1.50-1.75), p<0.0001 | 1.69 (1.53-1.87), p<0.0001 | 1.59 (1.45-1.76), p<0.0001 |
| Age <35 years   | 2.03 (1.80-2.31), p<0.0001 | 2.19 (1.86-2.57), p<0.0001 | 2.10 (1.79-2.45), p<0.0001 |
| 35 years ≤age <40 years   | 1.51 (1.36-1.68), p<0.0001 | 1.52 (1.33-1.75), p<0.0001 | 1.46 (1.28-1.67), p<0.0001 |
| 40 years ≤age <45 years   | 1.19 (1.02-1.23), p=0.015  | 1.10 (0.97-1.24), p=0.14   | 1.10 (0.98-1.24), p=0.119  |
| 45 years ≤age <50 years   | 1 (ref)                    | 1 (ref)                    | 1 (ref)                    |
| Age ≥50 years   | 0.80 (0.70-0.92), p=0.002  | 0.77 (0.63-0.93), p=0.008  | 0.84 (0.33-1.00), p=0.058  |
| 1-3 nodes   | 1.67 (1.52-1.84), p<0.0001 | 2.18 (1.88-2.53), p<0.0001 | 2.02 (1.76-2.33), p<0.0001 |
| ≥4 nodes  | 3.23 (2.92-3.57), p<0.0001 | 5.14 (4.43-5.97), p<0.0001 | 4.68 (4.07-5.39), p<0.0001 |
| Tumour size > 2 cm  | 1.75 (1.62-1.89), p<0.0001 | 2.27 (2.04-2.52), p<0.0001 | 2.21 (1.99-2.44), p<0.0001 |
| BMI >30 kg/m <sup>2</sup>   | 1.25 (1.12-1.39), p<0.0001 | 1.38 (1.20-1.58), p<0.0001 | 1.41 (1.24-1.61), p<0.0001 |
| <b>Multivariate models</b>  |                            |                            |                            |
| Age ≤40 years   | 1.60 (1.49-1.73), p<0.0001 | 1.65 (1.49-1.83), p<0.0001 | 1.56 (1.42-1.72), p<0.0001 |
| 1-3 nodes   | 1.56 (1.42-1.73), p<0.0001 | 1.97 (1.70-2.30), p<0.0001 | 1.84 (1.59-2.12), p<0.0001 |
| ≥4 nodes  | 2.89 (2.60-3.21), p<0.0001 | 4.34 (3.72-5.07), p<0.0001 | 3.96 (3.43-4.58), p<0.0001 |
| Tumour size > 2 cm  | 1.48 (1.37-1.60), p<0.0001 | 1.79 (1.61-2.00), p<0.0001 | 1.76 (1.58-1.95), p<0.0001 |
| BMI >30 kg/m <sup>2</sup>   | 1.14 (1.02-1.27), p=0.018  | 1.24 (1.08-1.42), p=0.002  | 1.28 (1.12-1.46), p<0.0001 |
| Reference categories are age >40 years (age 45-49 for 5-year age groups), node-negative, tumour size ≤2 cm, and BMI ≤30 kg/m <sup>2</sup> . Patients with missing values were assigned to an unknown group in the multivariate model. |                            |                            |                            |
| Table 3: Hazard ratios (95% CI) for outcomes by age, nodal status, tumour size, and BMI in univariate and multivariate Cox models for women with hormone-receptor-positive cancer   |                            |                            |                            |

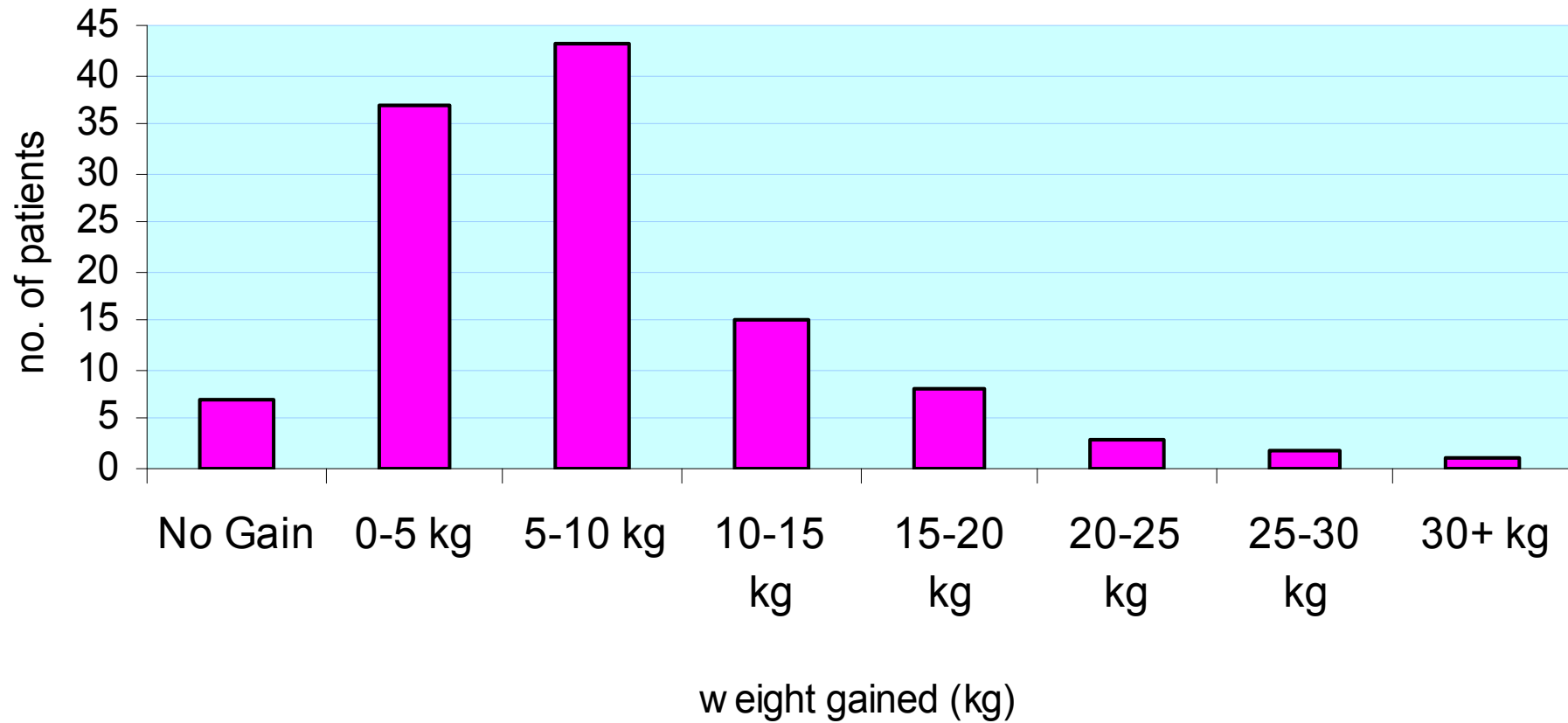
# Obese and diabetics do worse: Why?

- Treatment related?
- Perturbed energy balance?

Maximum Wt gain in breast cancer survivors in a series of clinical trials at RBH

### Maximum Weight Gain from Baseline

*n=116*



# Is weight gain a concern?

## Increased levels of adiposity:

- **↑ Breast cancer risk in postmenopausal women**  
(1.29, 95%CI: 1.22,1.36)
- **Poorer cancer prognosis:**
  - **↑ risk of recurrence** (1.78, 95%CI: 1.50, 2.11)
  - **↑ risk of death** (1.36, 95% CI: 1.19, 1.55)

## Weight gain of +3 kg:

- **↑ risk of recurrence** (1.4, 95%CI: 1.02, 1.92)
- **↑ risk of death** (1.35, 95%CI: 1.00, 1.82)

# Breast Cancer and Glucose Tolerance

- 39 women non diabetic women, age 59+/- 13 years
- 6 cycles **FEC** X3 and/or  
**Docetaxel** X3 or 6 cycles of **FEC**
- **Dexamethasone** 8mg PO immediately before **FEC**
- **Dexamethasone** 8mg PO 24 hours, 12 hours and immediately before **Docetaxel**
- 6 developed impaired GT & 8 glucose within diabetic range

•Hickish et al JNCI 2009

# **Factors associated with weight gain after breast cancer**

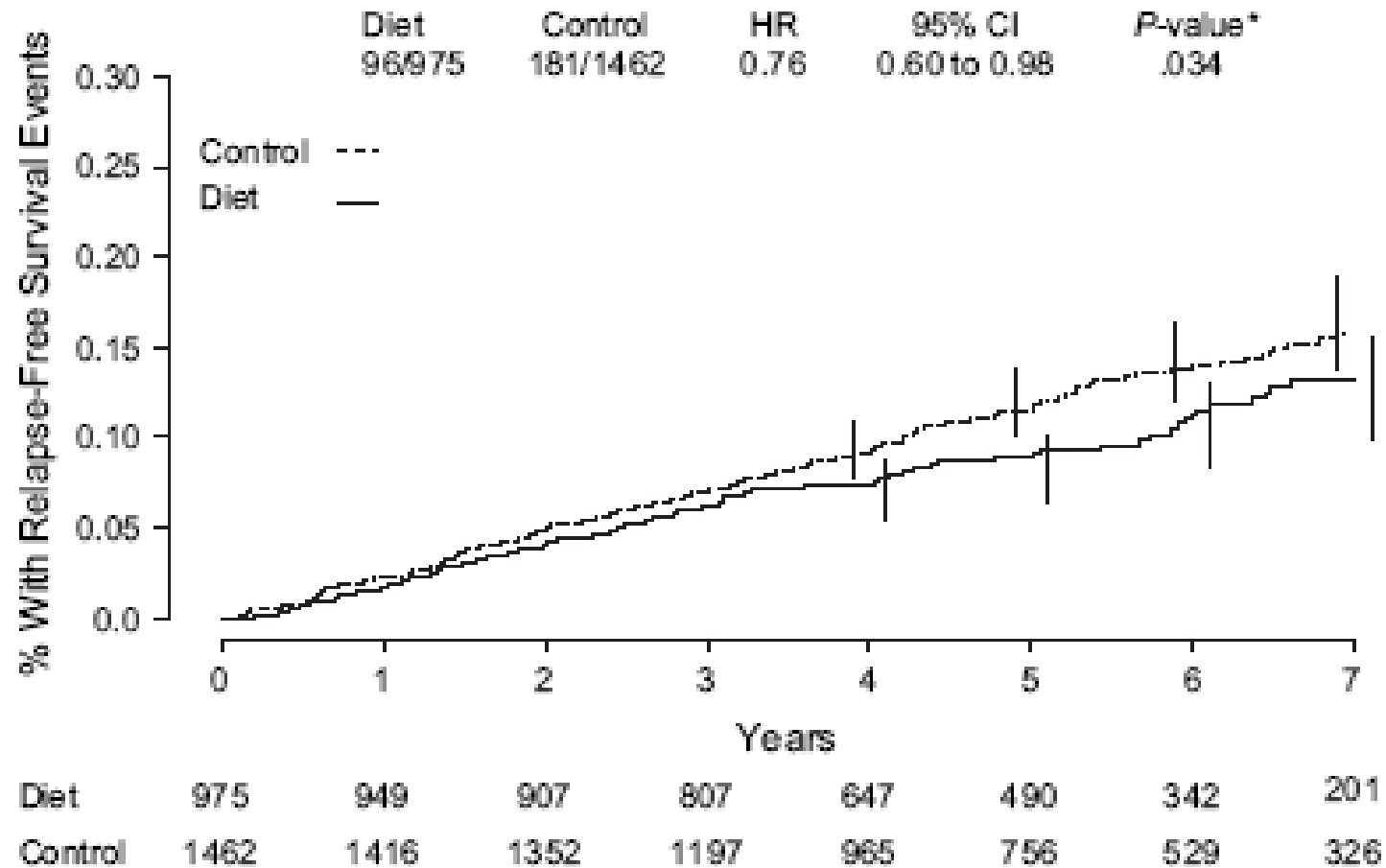
- **Explored factors: treatment and lifestyle**

**No conclusive data:**

- **Different treatments used**
- **Anti-oestrogen therapy (Tamoxifen and Aromatase Inhibitors)**
- **Large length of periods between weight measures**
- **Bias: self selection, social desirability**

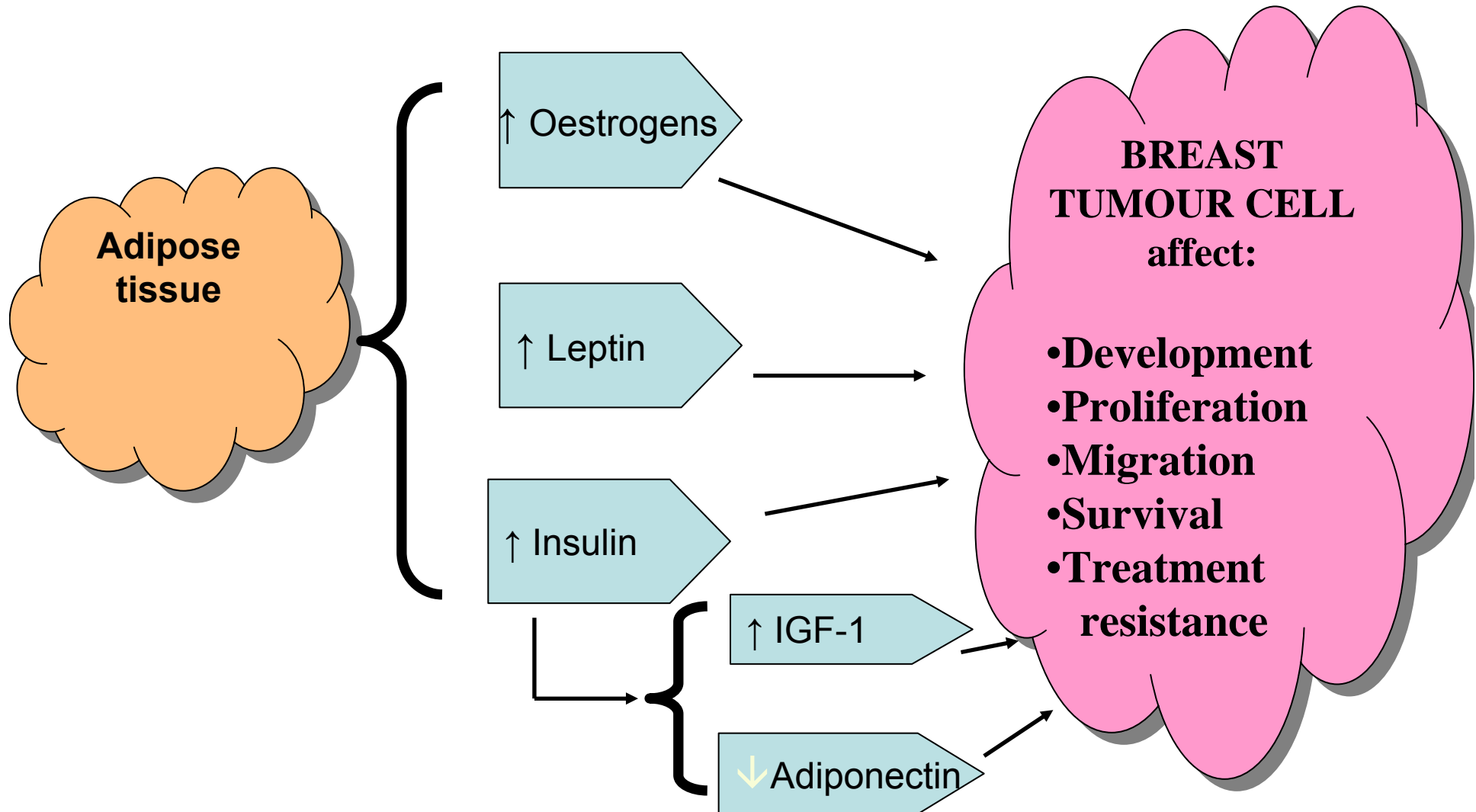
- **Unexplored factors for weight gain after cancer**
  - **Genes related to common forms of obesity: FTO, Mc4R**
  - **Effect of treatment on hormones and cytokines regulating body weight homeostasis: leptin, ghrelin, insulin, adiponectin**

# WINS Study

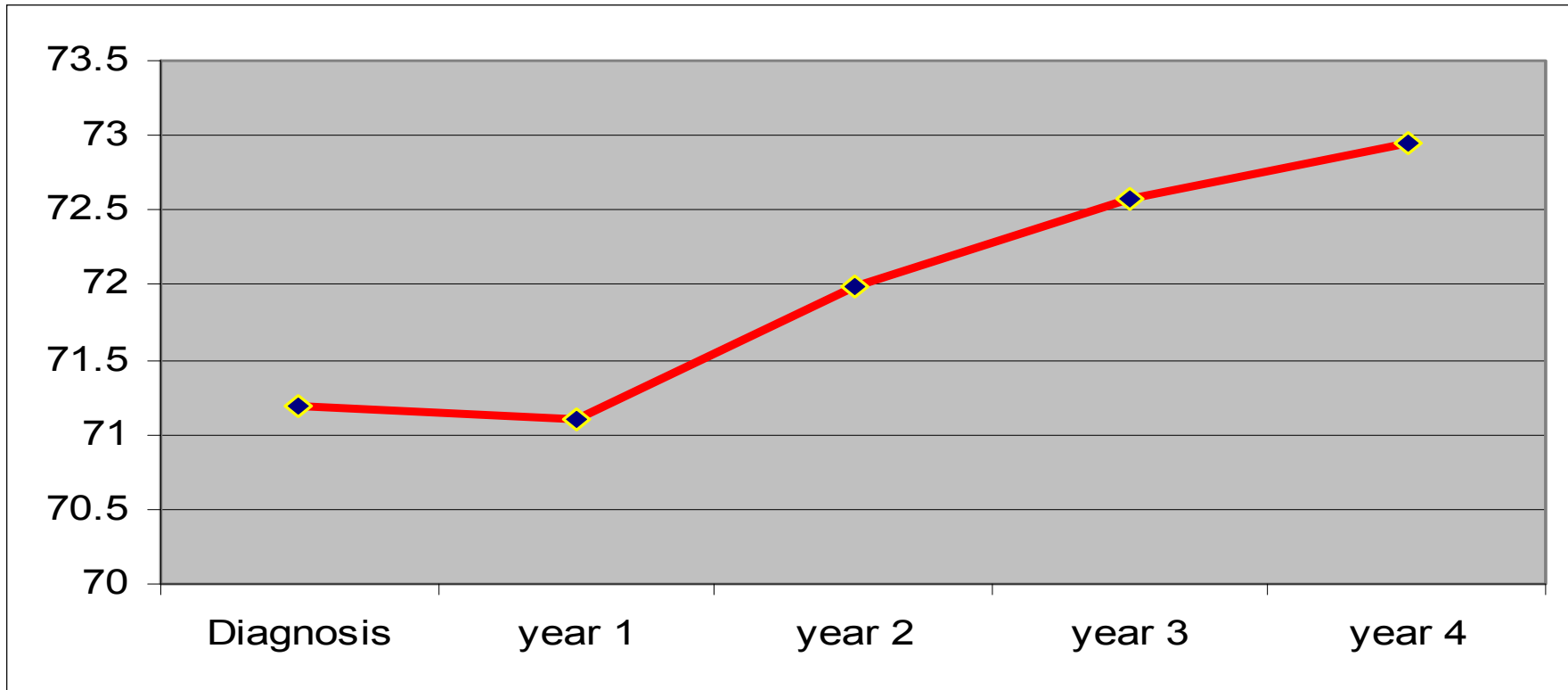


JNCI 2007

# Association between adiposity and breast cancer



# Weight (kg)



## Not associated with:

- Chemotherapy or Tamoxifen
- Menopausal variables
- Age
- Genes related to obesity

## Associated with:

- Aromatase inhibitors
- ***STUDY ONGOING***

Barberia A et al 2009  
unpublished

# Epigenetics - Insulin resistance and muscle

- Muscle requires energy – mitochondria
- Study of epigenetic changes in patients with insulin resistance
- Methylation of PGC-1 - involved in mitochondrial development
- In experimental models – culture conditions mimicking poor diet/obesity  
>>Methylation of PGC-1

» Zierath et al Cell Metabolism 2009

# Life style and cancer

- Inter play between cancer cells and the host
- Adipose tissue – an active organ
- Muscle – produces cytokines
- Oestrogen
- Insulin axis
- Inflammation related cytokines
- Host genetics....influence of environment/food
- Brain influences life style

# Survivorship

- Return to normal function
- Physical
- Psychological
- Lifestyle
- Economic

# Understanding biology

- Causes – genetics, environment, epigenetics
- Genetic risk profile
- Prevention...
- ....by surgery....colon, breast ovaries
- ....by drugs ... tamoxifen, ??aspirin
- ....by lifestyle

# Patient centred

- Patient partnership panel
- Patient representation on Lead Clinicians Group
- Patient membership of tumour groups
- Research – patients input ..? relevance
- Community Services....chemotherapy

# Getting the basics right

- Early presentation
- Sometimes no symptoms until late and advanced state of disease
- Often symptoms long before seeking advice....'coping' 'it'll go away' embarrassment, lack of time,
- Fatalism
- Early recognition and referral

# FTO Gene

- Identified by genome wide scan.
- 40,000 individuals
- Single Nucleotide Polymorphism linked to obesity
- Doubles risk of becoming obese

Science 2007

# Breast Cancer and Diabetes

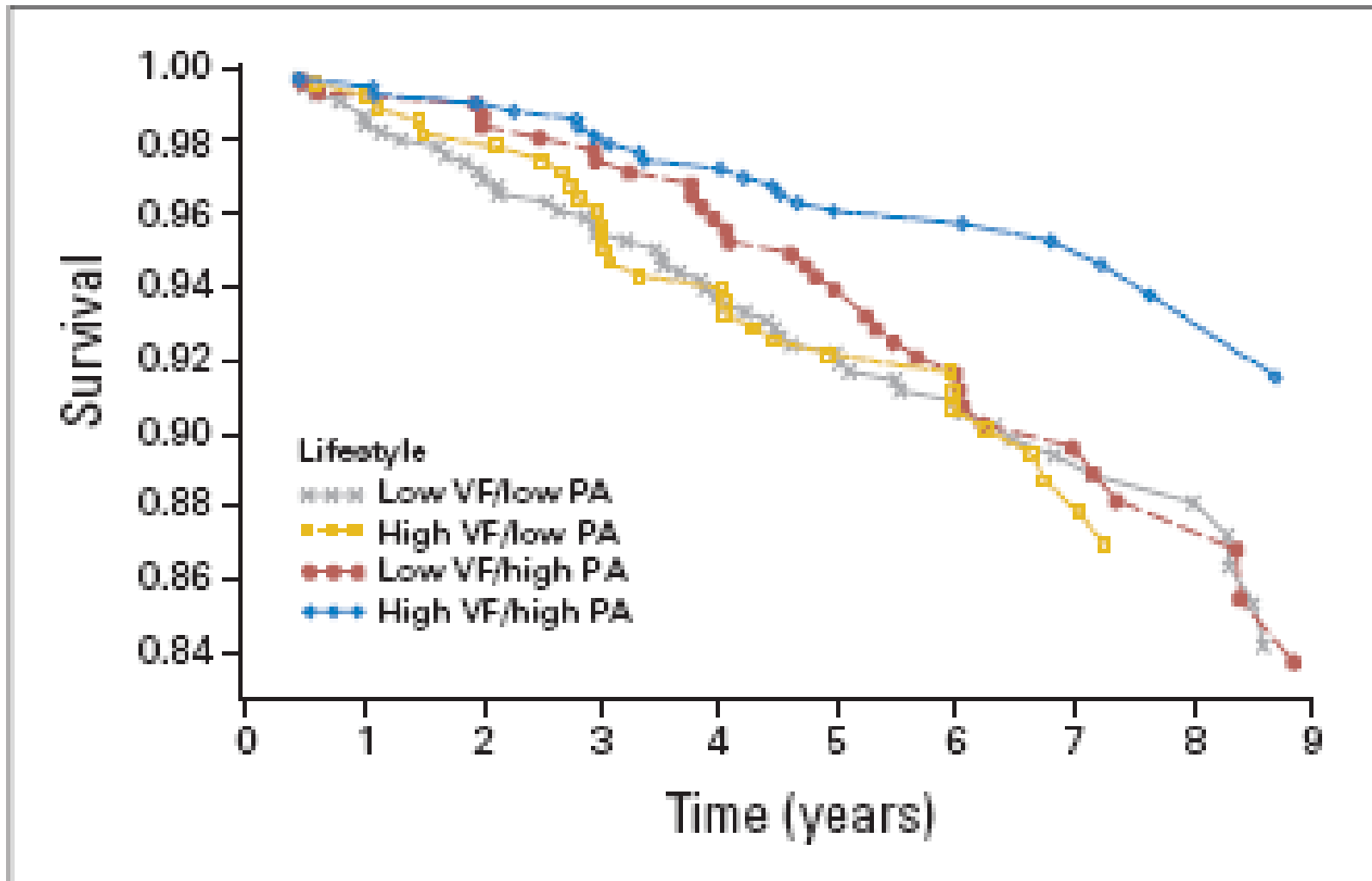
- Diabetes is associated with increased risk of breast cancer<sup>1</sup>
- Within 5 year mortality in diabetic women with breast cancer is increased by 40%<sup>2</sup>
- Excess weight gain is common in women after adjuvant chemotherapy for breast cancer
- Obesity and diabetes are closely linked and obesity is a negative prognostic factor in women with breast cancer
- ? Related to oestrogen and adipocytokines (leptin, adiponectin) and insulin resistance<sup>3</sup>

<sup>1</sup>Int J Cancer 2007; 121:856, <sup>2</sup>Breast Cancer Res Treat 2007, July 21<sup>st</sup> [Epub ahead of print], <sup>3</sup>BMJ 2005; 366: 1108.

# Breast Cancer and Glucose Tolerance

- Hyperglycaemia is associated with increased morbidity and mortality in many acute and chronic medical conditions
- Hyperglycaemia causes unpleasant osmotic symptoms
- The consequences of acute hyperglycaemia on the response to cancer chemotherapy is not known
  
- **Aim: To determine if adjuvant chemotherapy for breast cancer is associated with acute hyperglycaemia**

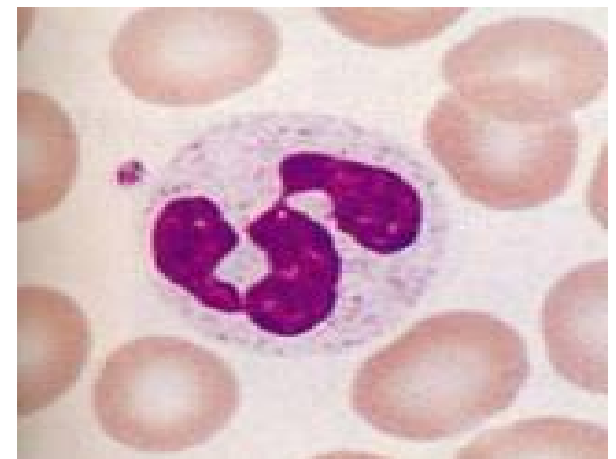
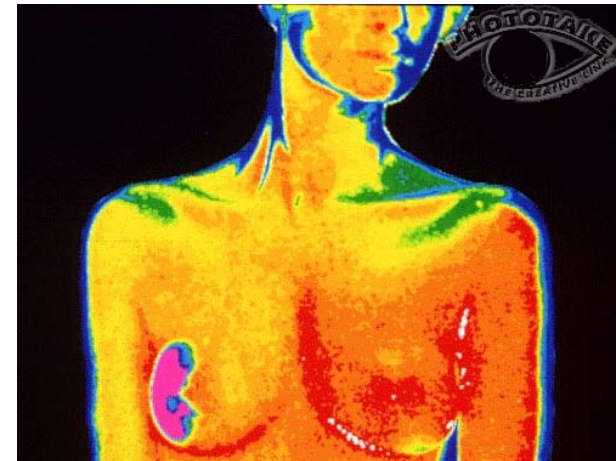
# WHEL study - Breast Cancer Survivors



VF = vegetables and fruit; PA = physical activity

# Breast Cancer and Glucose Tolerance

- Non-diabetic women with breast cancer
- Adjuvant chemotherapy
- Blood glucose levels prior to and at the end of each infusion of chemotherapy
- WCC on day 10



# Understanding biology, new drugs

- Understanding cancer cells...DNA, RNA and proteins
- Designing new drugs

# Prevention by removing lifestyle risks

- Smoking
- Environmental pollutants...assessment of risk
- obesity

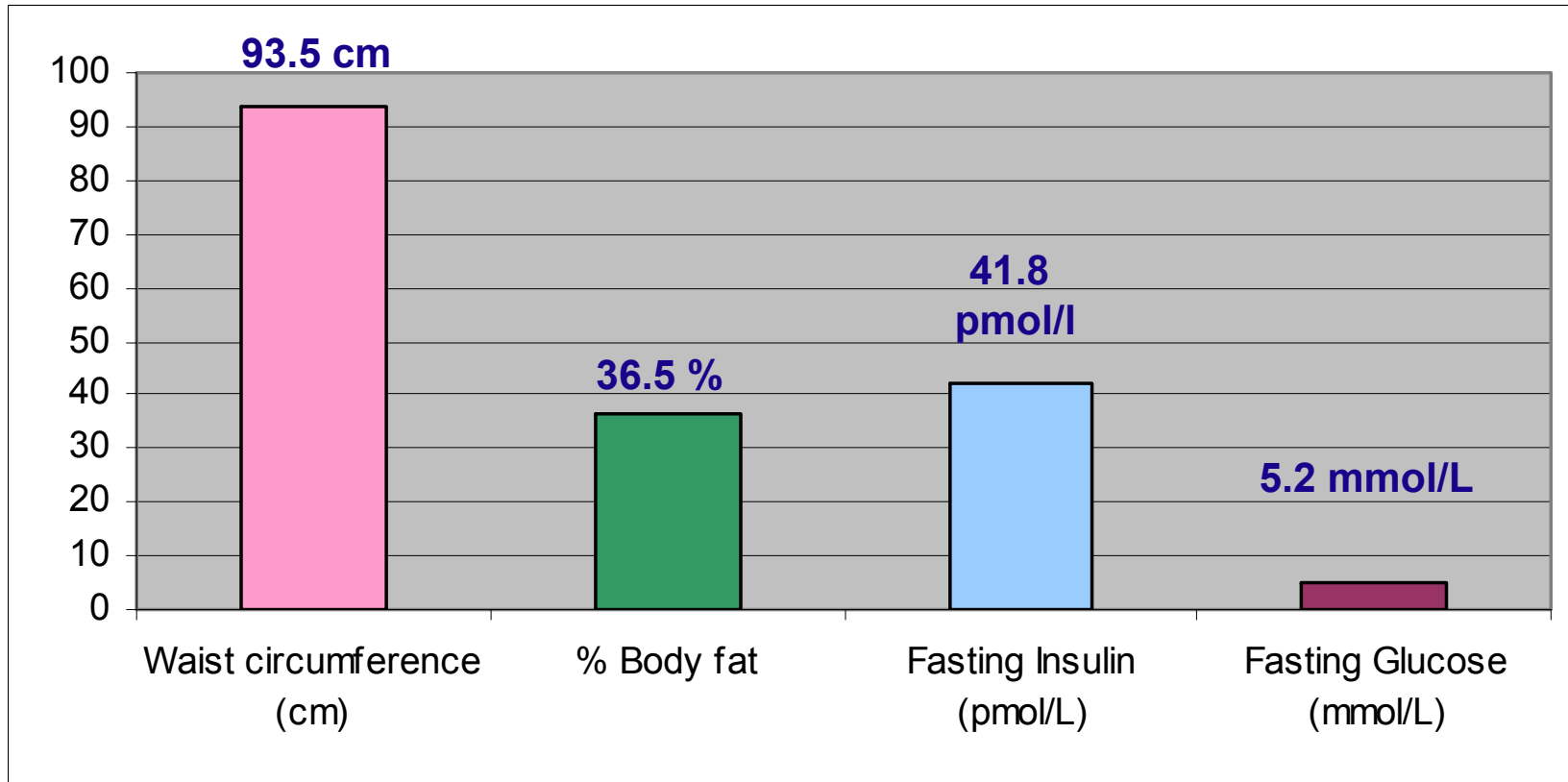
# Getting the basics right

- **Organisational**
  - Cancer Plan
  - 'Waiting times' agenda...levers for change
  - Cancer Networks.....Dorset CN
  - Equity of access, equity of quality
  - Multi disciplinary teams within hospitals
  - Tumour site specific groups across Network
  - Peer Review...Manual of Cancer Standards
  - NICE
  - Research ...at the centre of 'service'
- **Treatment ...**

# Is anything safe to eat? Cancer report adds bacon, ham and drink to danger list



Daily Mail Wednesday 31<sup>st</sup> October



## Not associated with:

- Age
- Menopausal variables
- Genes associated with obesity
- Chemotherapy or tamoxifen
- Aromatase inhibitors (% fat and glucose)

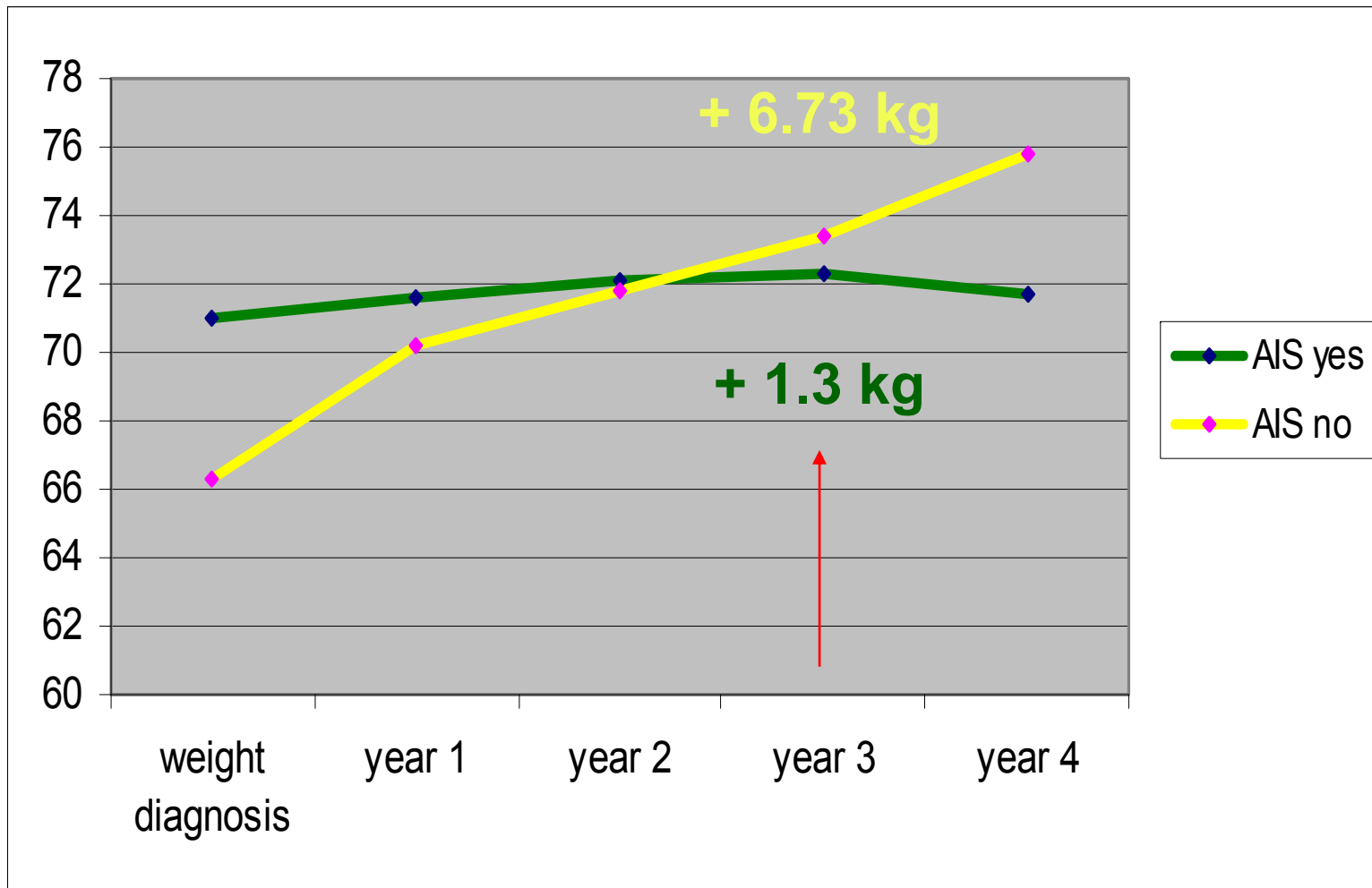
# Aims



**To identify:**

- **Factors associated with weight gain with breast cancer treatment**
- **Metabolic consequences of weight gain**

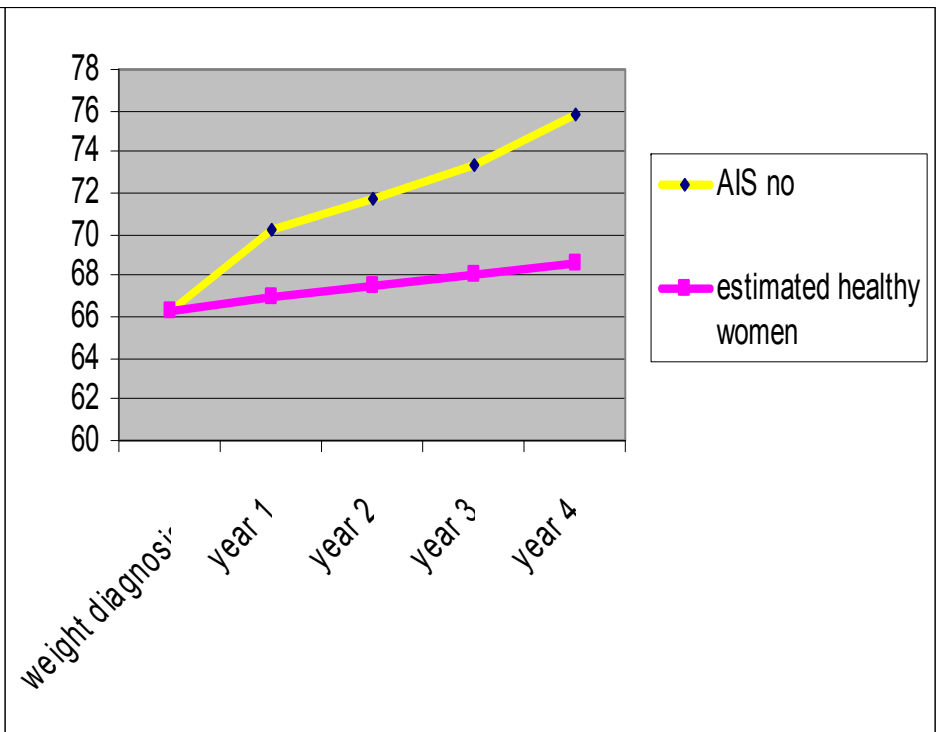
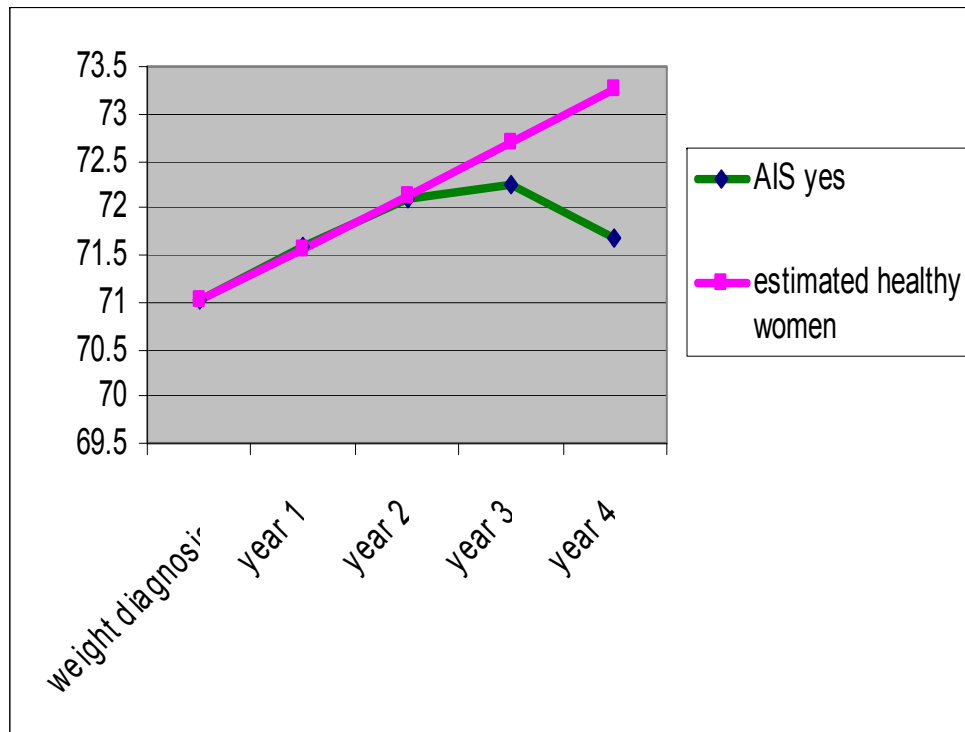
# Aromatase Inhibitors



# Compared with cohort of healthy women

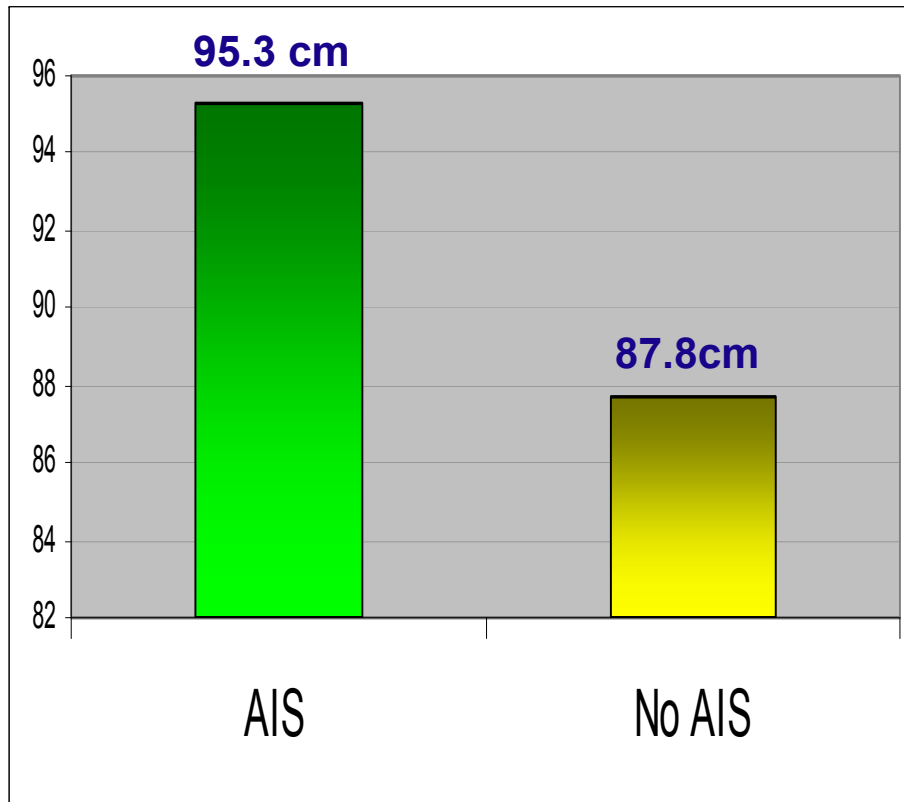
## Aromatase Inhibitors

## No Aromatase Inhibitors

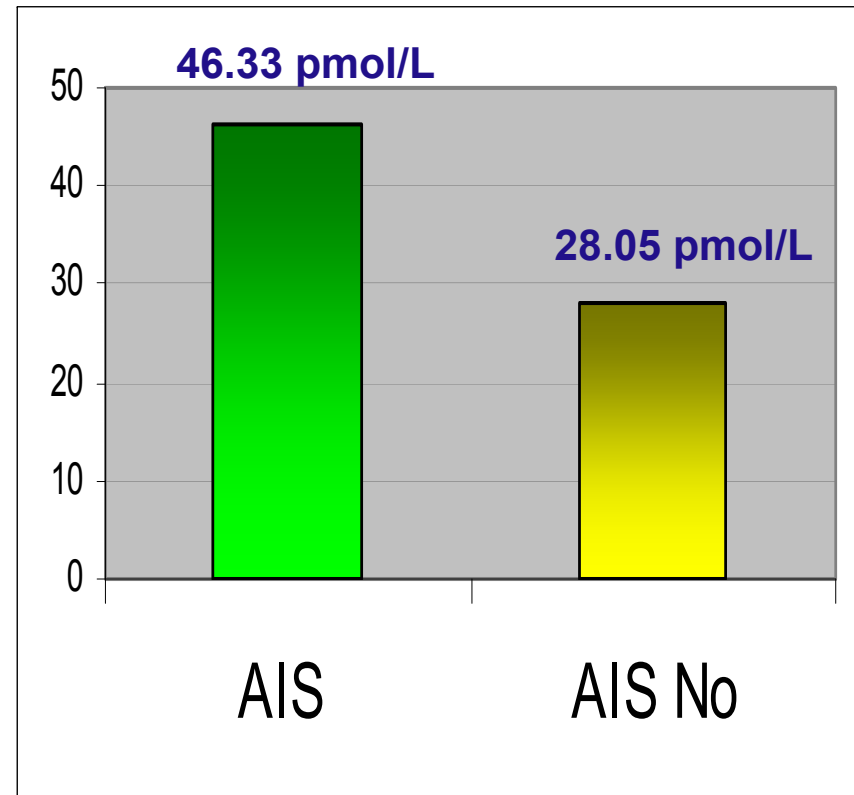


# Aromatase Inhibitors

## Waist circumference



## Fasting insulin levels



Barberia A et al 2009 unpublished

# **CONCLUSIONS (so far!)**

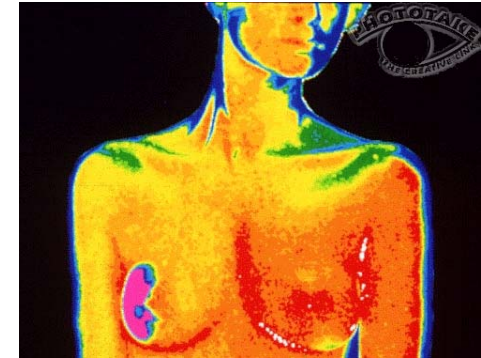
- **Some group of participants gained weight after diagnosis (compared to background population of healthy women)**
- **Aromatase Inhibitors use seems to contribute to:**
  - **less weight gain after diagnosis**
  - **greater waist circumference at study entry**
  - **higher fasting insulin levels at study entry (?prognostic implications)**

# Limitations

- Small sample size
- Different machines used to record weight
- ? Self-selection bias
- Participants might have tried to lose weight
- Those who gained most weight might have been excluded because of recurrence or death.
- No data on waist circumference, fasting insulin and glucose at diagnosis



# Breast Cancer



- **Most common cancer in the UK: 126 new cases per day**
- **Incidence increasing since recording started due to:**
  - Screening programme
  - Exposure to sex hormones:
    - HRT use since the 90s
    - Obesity
- **PROBLEM:** Weight gain and/or increase in body fat after diagnosis?

Any questions?