

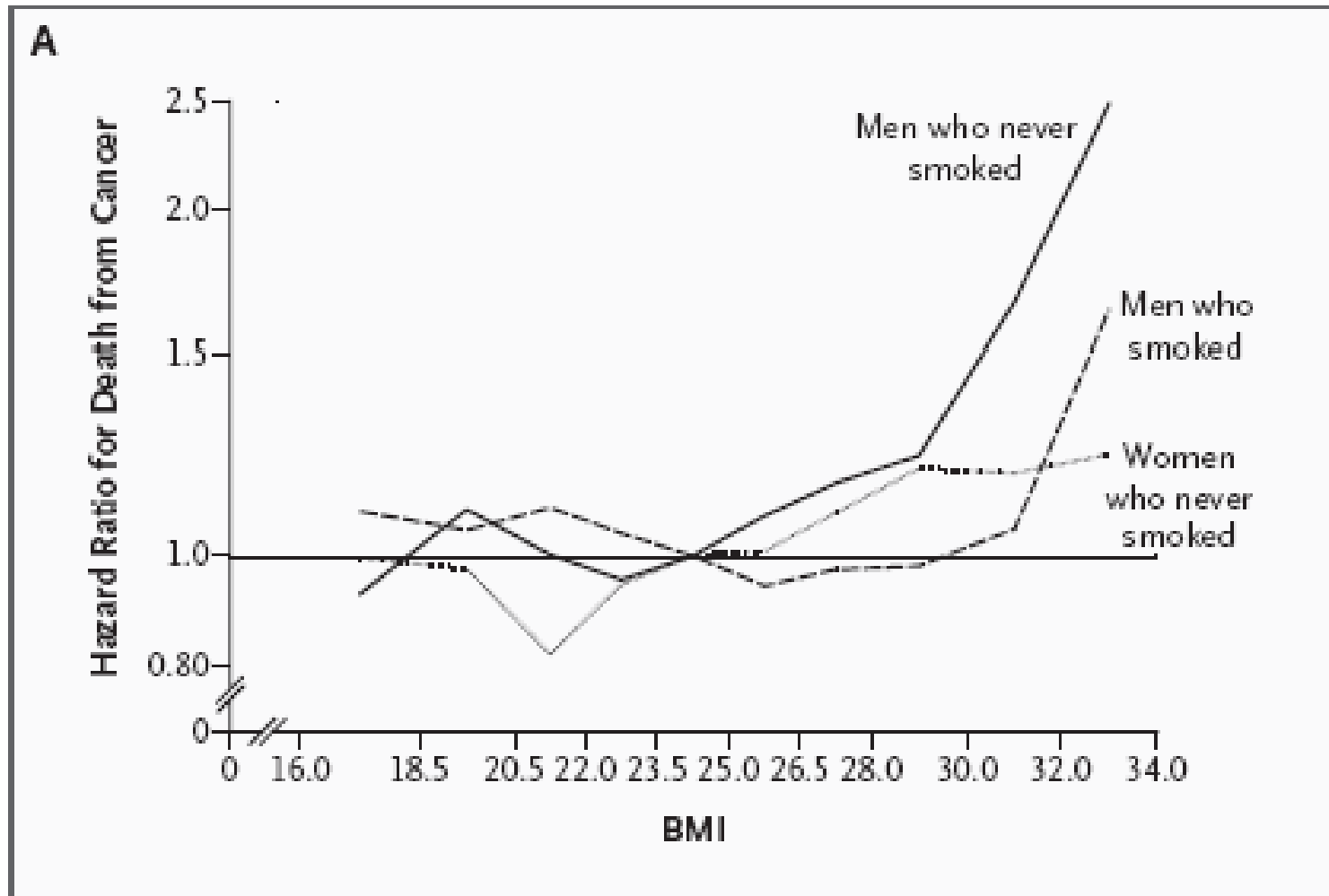
Tamas Hickish

Consultant Medical Oncologist
Poole and Bournemouth Hospitals
Visiting Professor Bournemouth University

Thanks to Delva Shamley, David Kerr,
Anton Parker, Peter Thomas,



BMI and risk of cancer death - Koreans



NEJM 2006

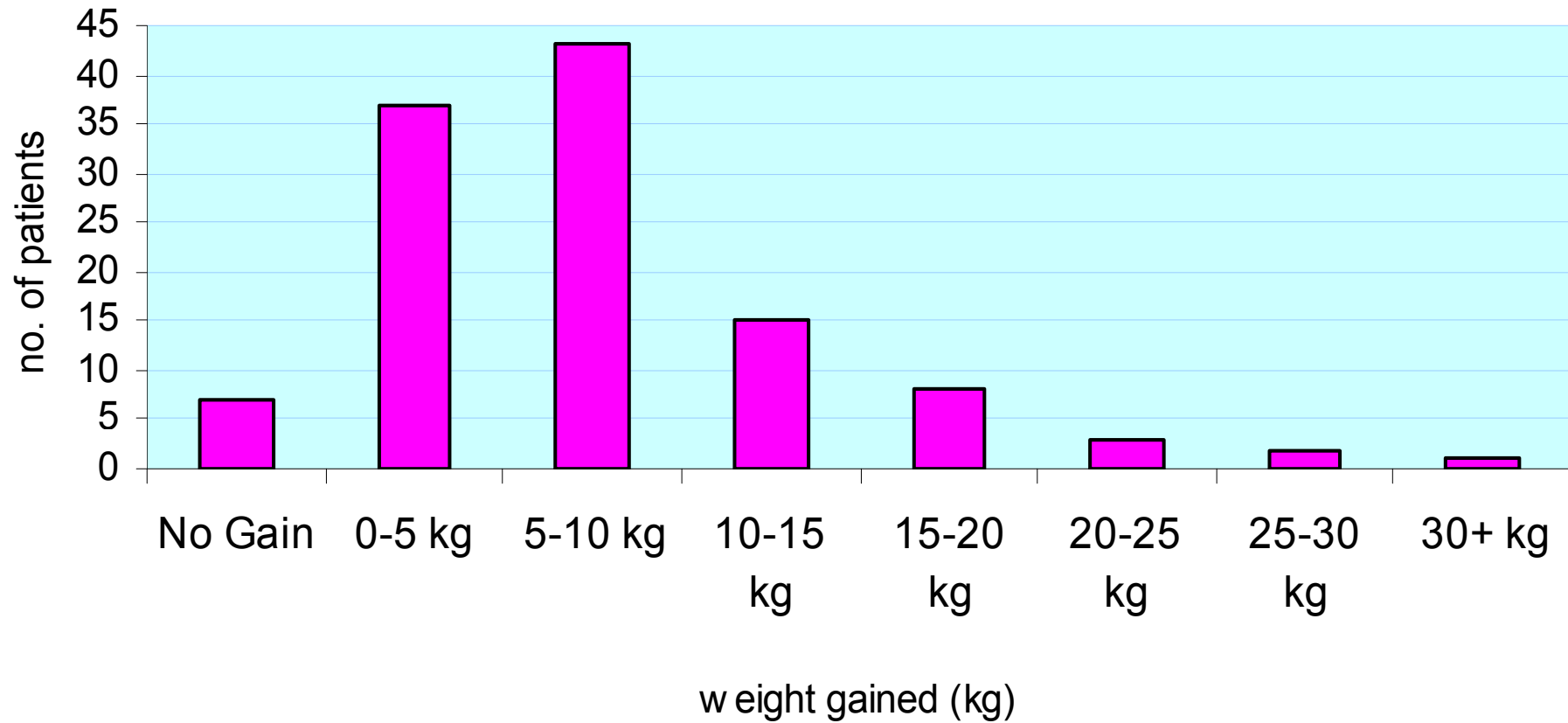
Meta-analysis of ovarian suppression as adjuvant therapy for breast cancer

	Recurrence	Death after recurrence	All deaths
Univariate models			
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	1.59 (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 (0.73-1.00), 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 ²	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
Multivariate models			
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 ²	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 ² . 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			

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

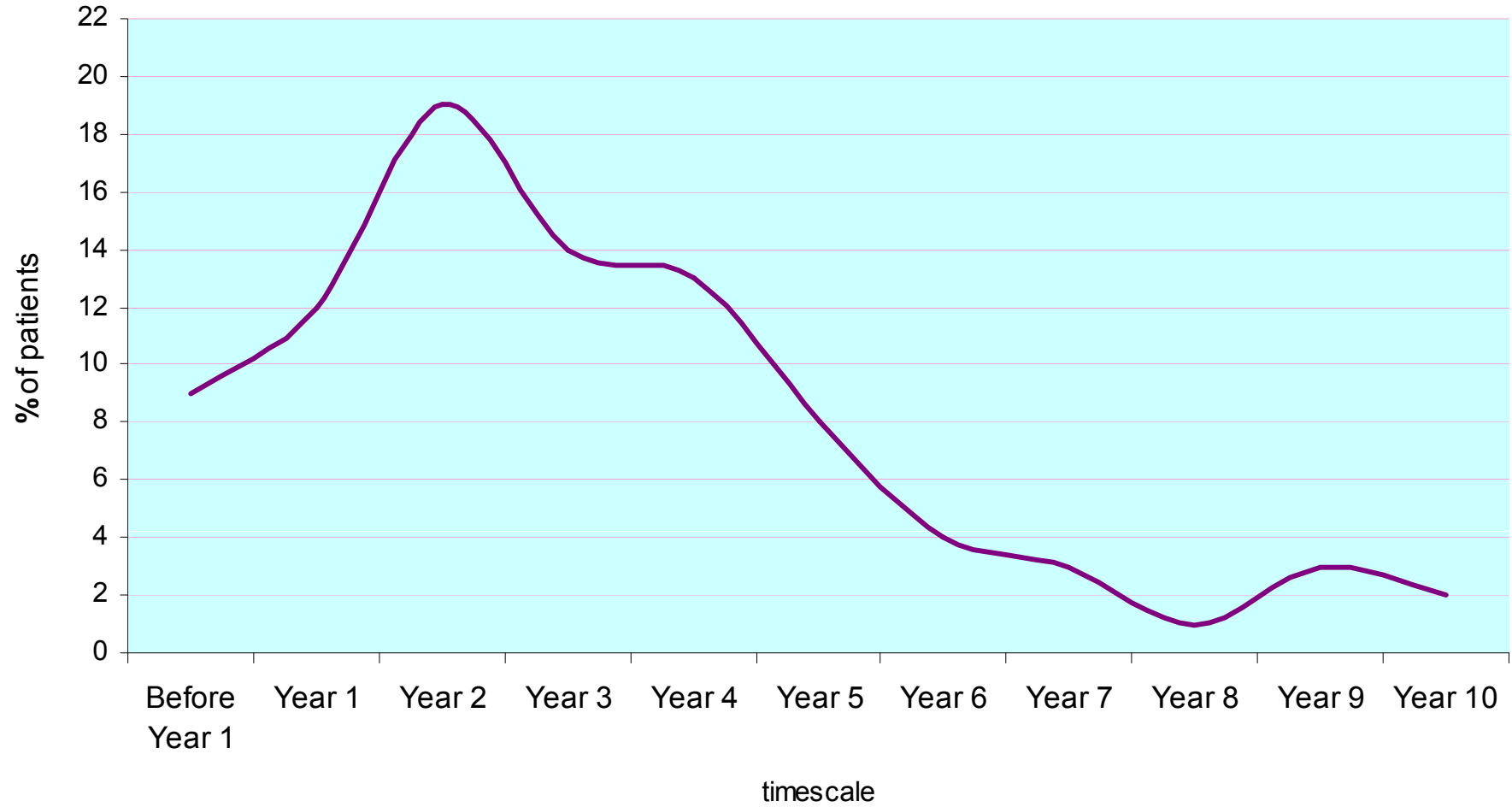
Maximum Weight Gain from Baseline

n=116



Year of Maximum Weight Gain

n=109

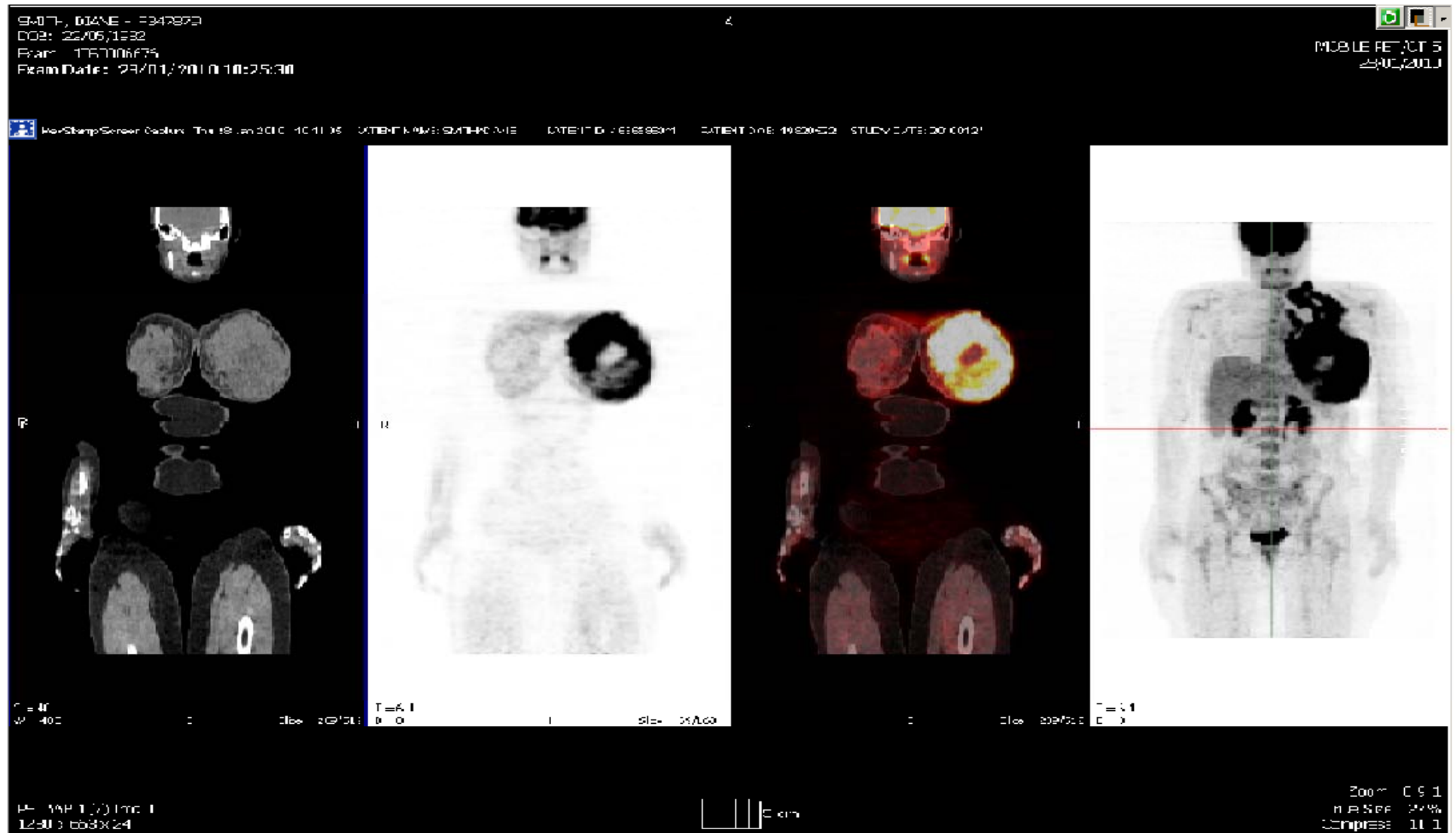


Breast Cancer and Diabetes

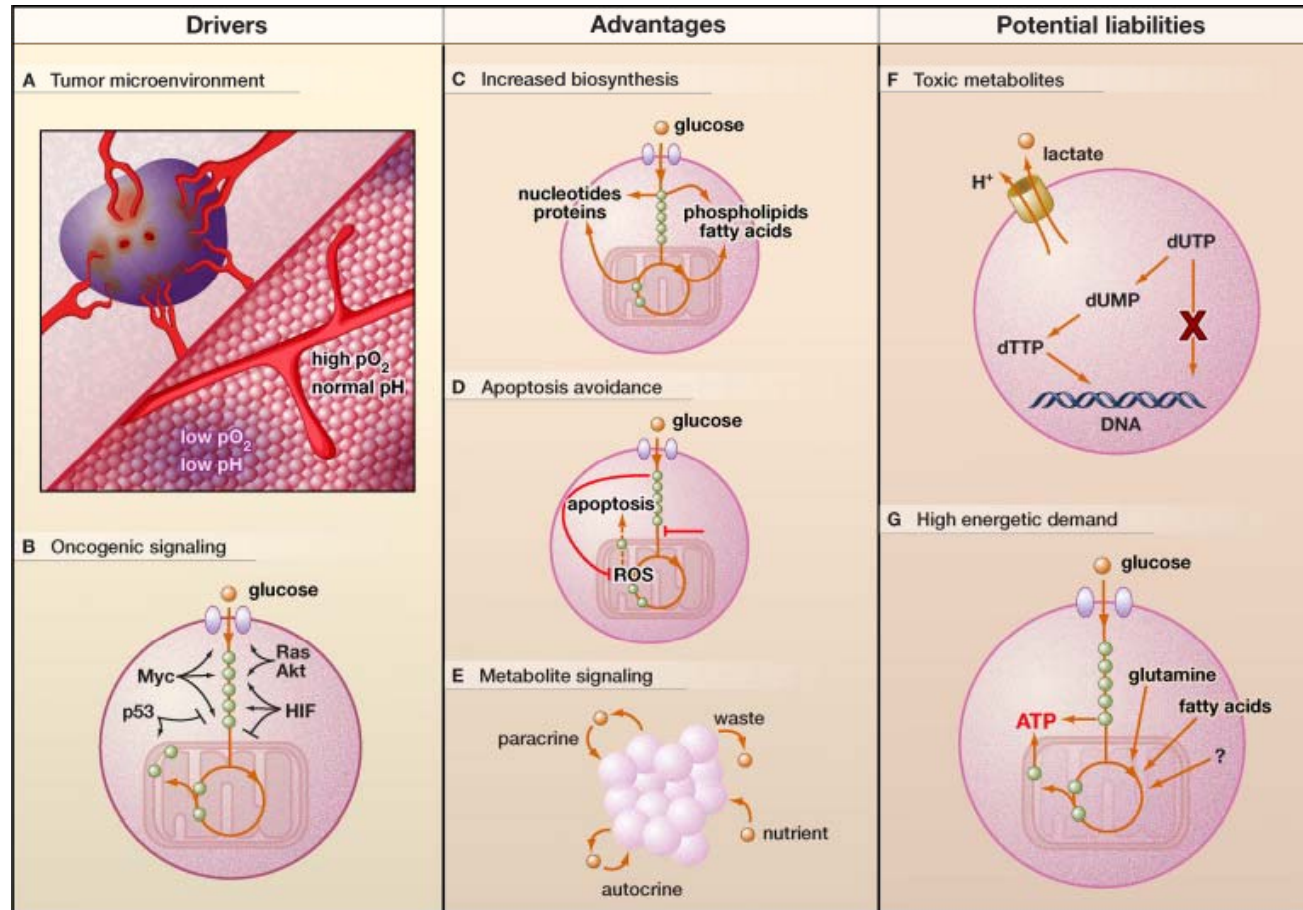
- Diabetes is associated with increased risk of breast cancer¹
- Within 5 year mortality in diabetic women with breast cancer is increased by 40%²
- Excess weight gain is common in women after adjuvant chemotherapy for breast cancer
- Obesity and diabetes are closely linked and obesity is a negative prognostic factor in women with breast cancer
- ? Related to oestrogen and adipocytokines (leptin, adiponectin) and insulin resistance³

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

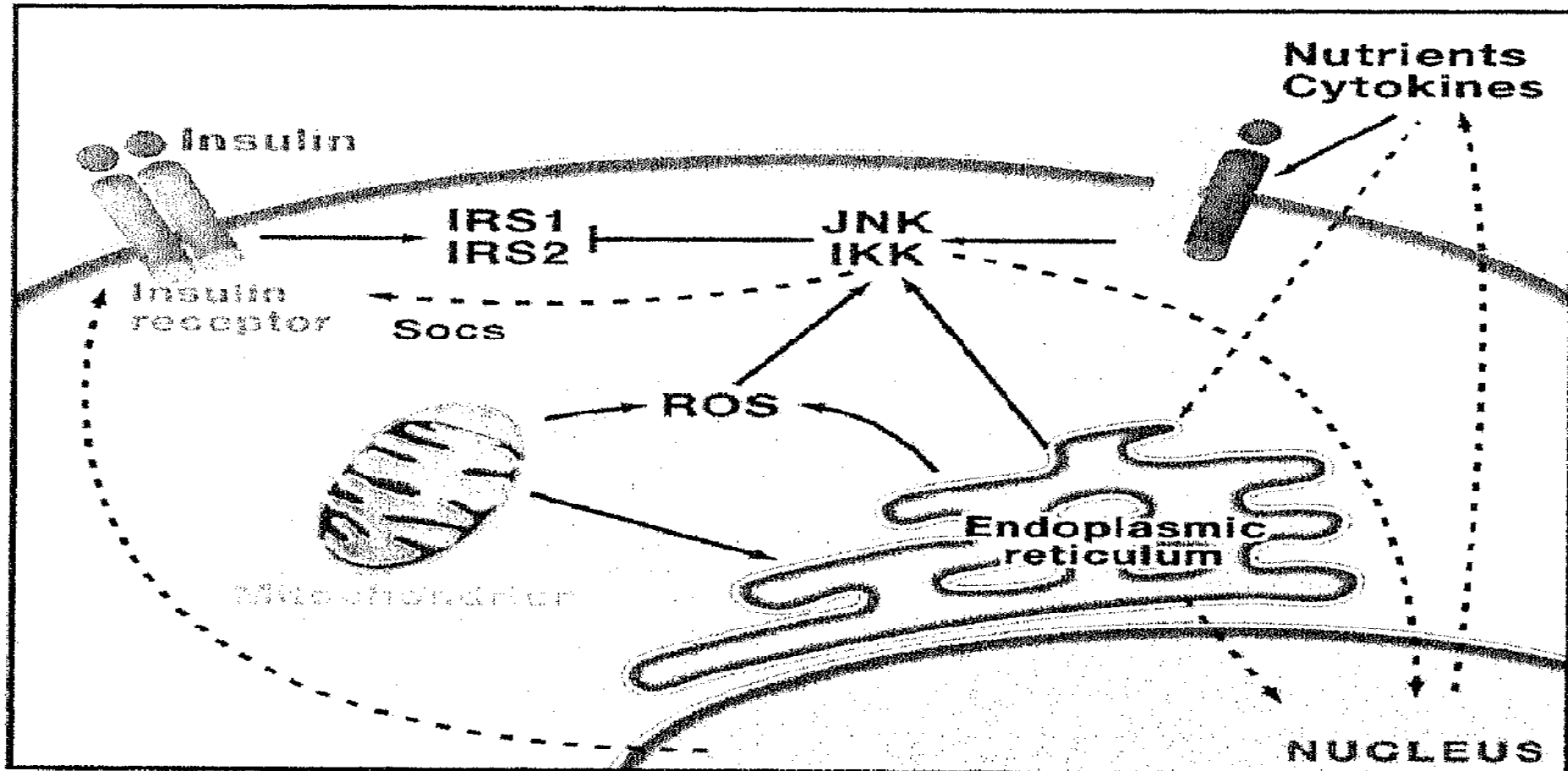
Aerobic Glycolosis



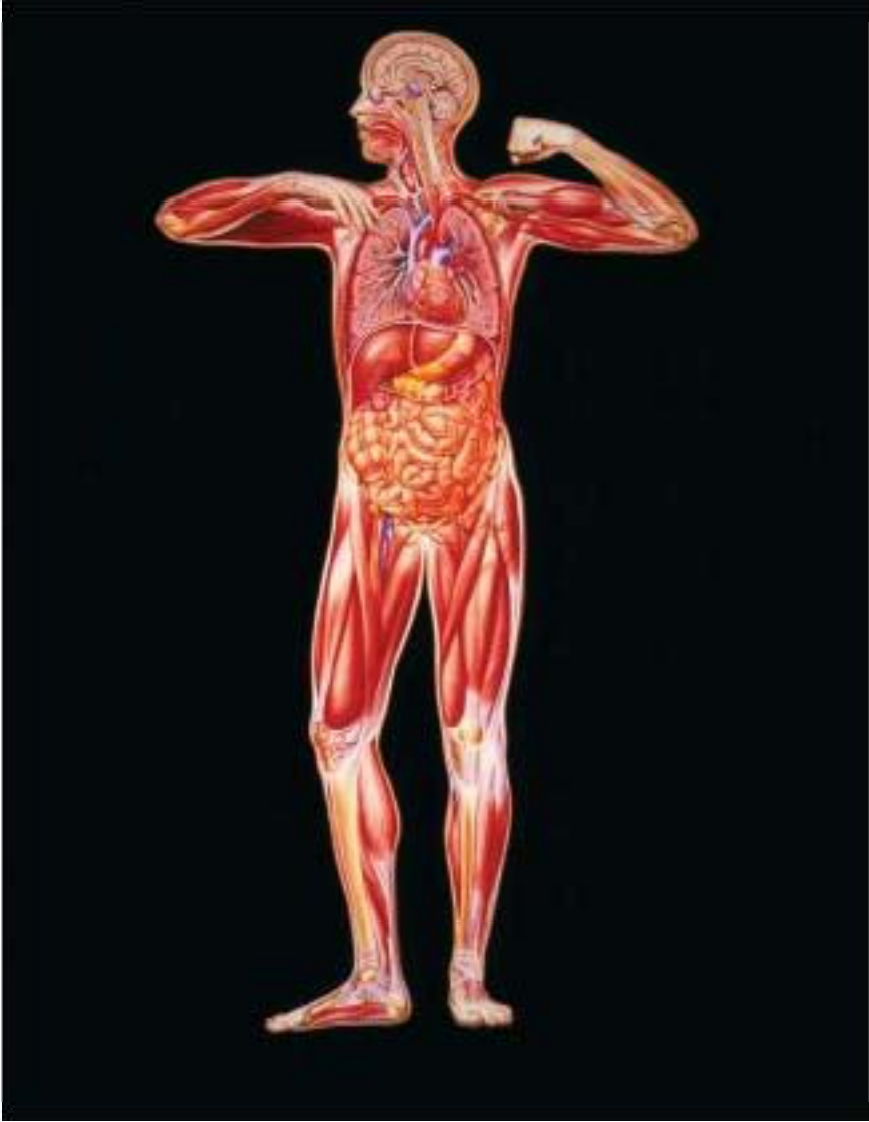
Cancer Cell Metabolism: Warburg and Beyond



Endoplasmic Reticulum – a nutrient sensor and determinant of inflammation



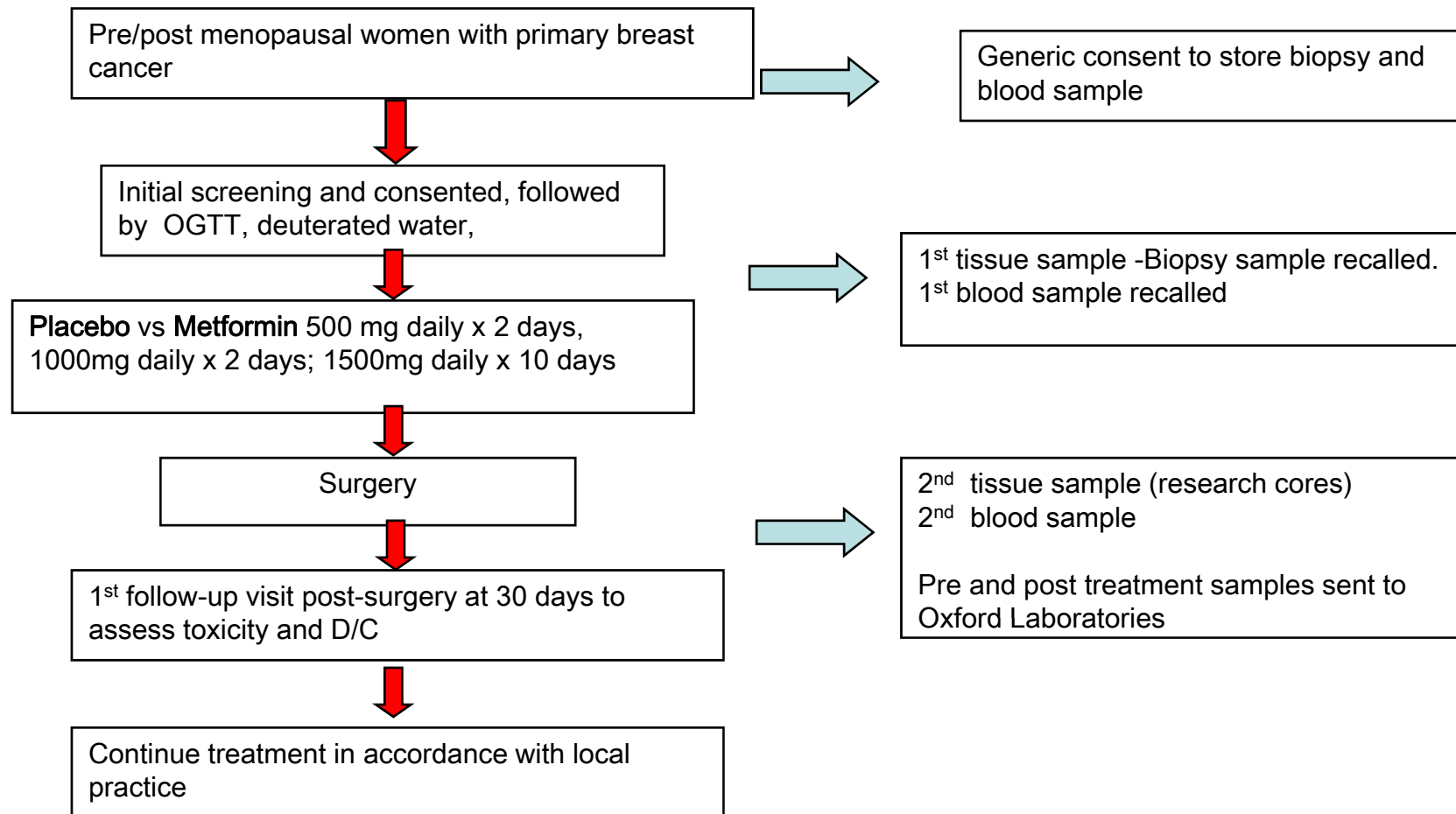
Hotasmigilil G. Cell 2010



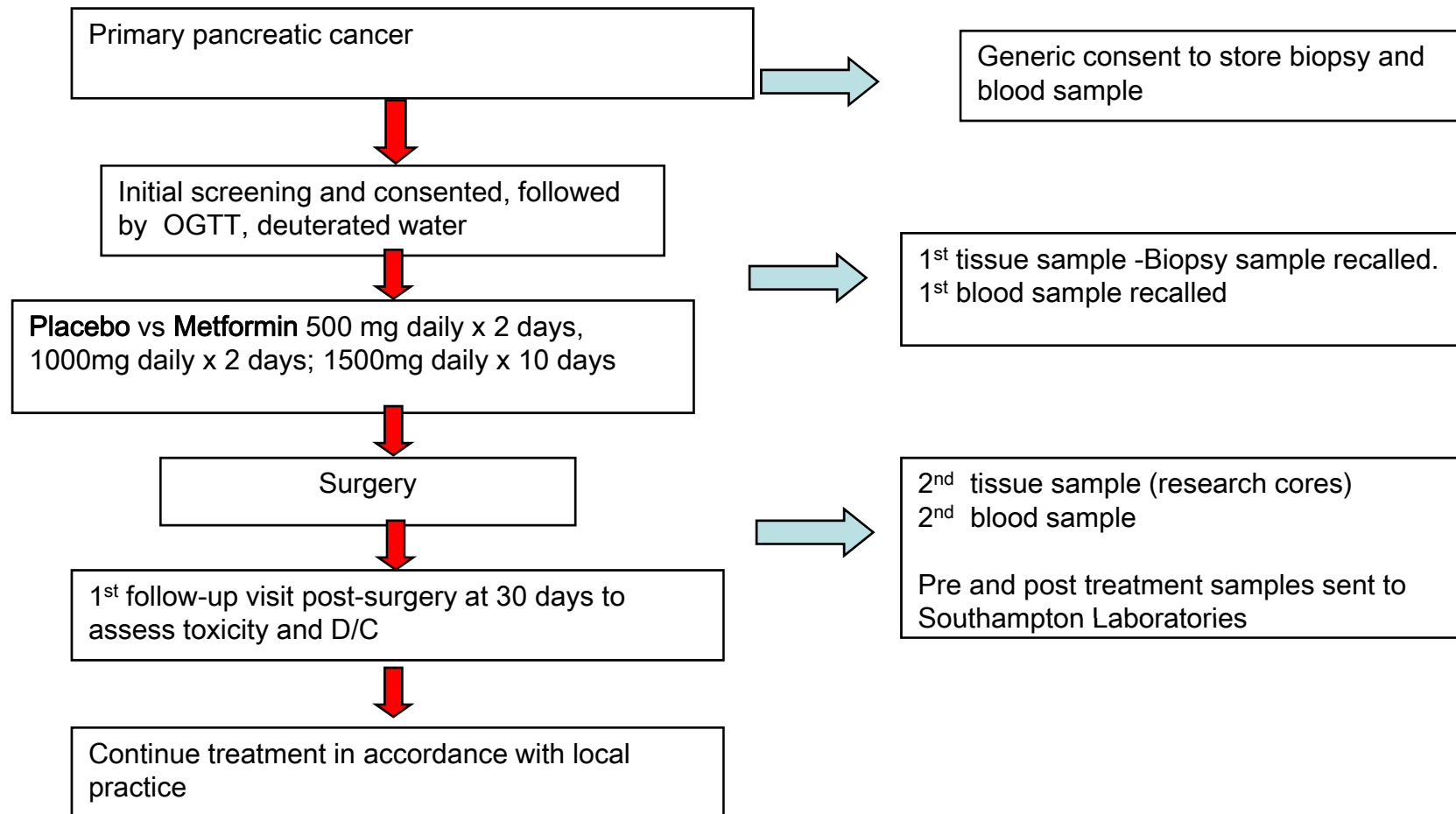
Metabolism and cancer development and progression

- Inter play between cancer cells and the host
- Adipose tissue – an active organ
- Nutrient sensing
- Oestrogen
- Insulin
- Inflammation related cytokines
- Immune function
- DNA repair
- Host genetics
- ***Explore these factors and pharmacological lifestyle interventions***

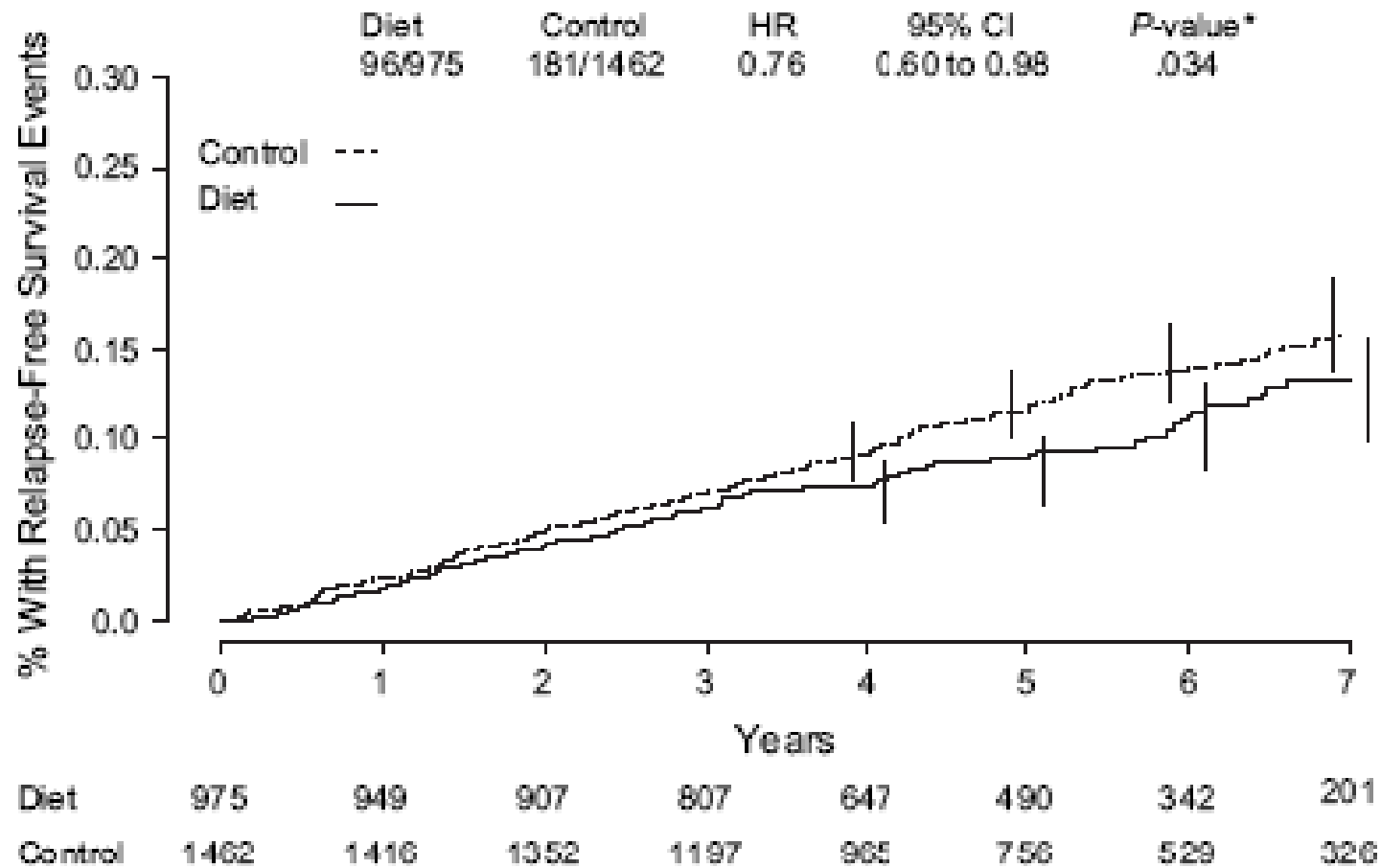
MetaB Trial – in collaboration with Adrian Harris, Oxford



MetaP Trial- in collaboration Surgical Unit Southampton

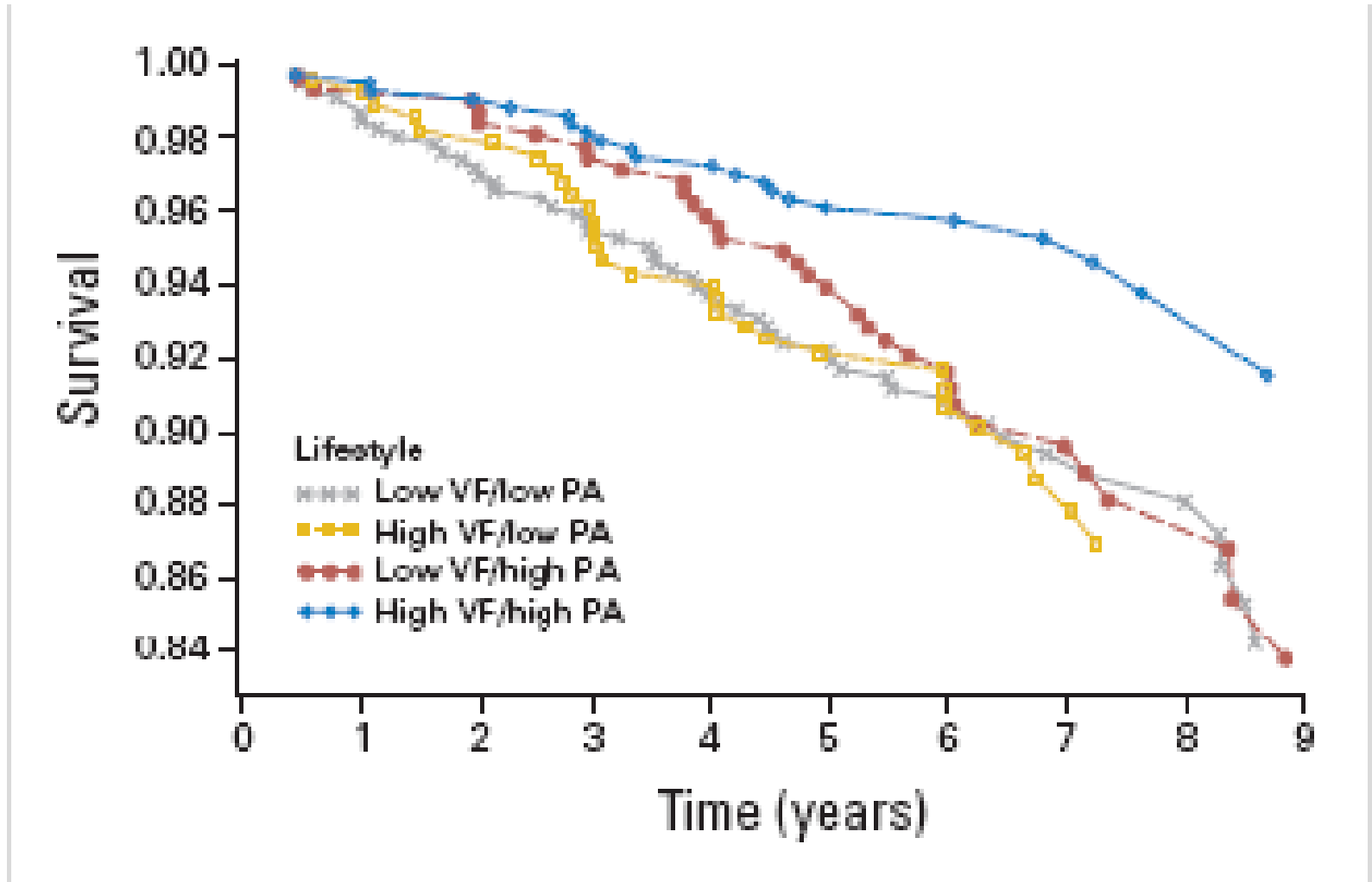


WINS Study

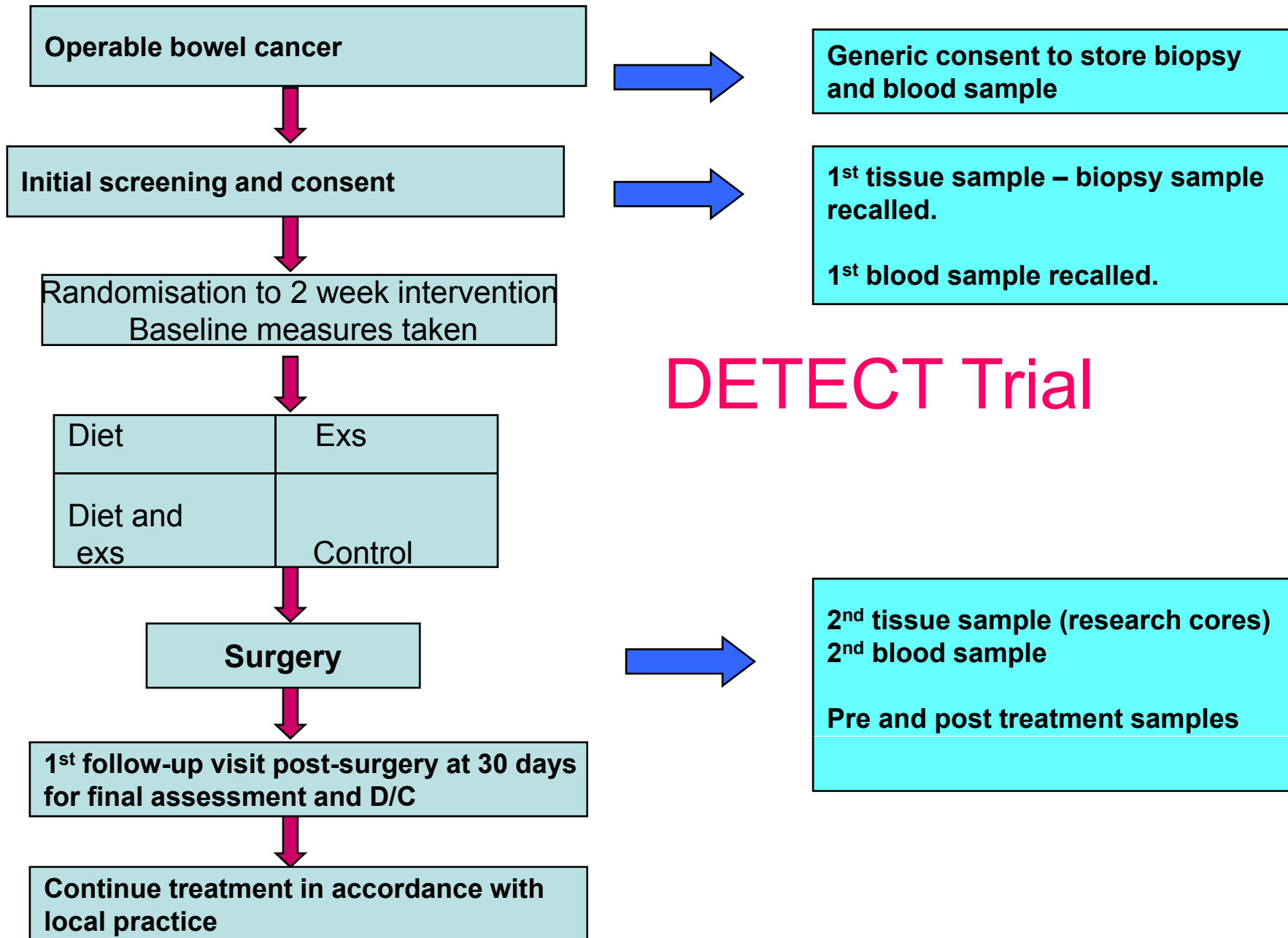


JNCI 2007

WHEL study



VF = vegetables and fruit; PA = physical activity



After Breast Cancer - Cross Sectional Study



To identify:

- **Factors associated with weight gain with breast cancer treatment - treatment type, genes..**
- **Metabolic consequences of weight gain**

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)**
 - **Now 215 patients recruited**
 - **Longitudinal Study approved – Jaana Jeffrey Phd Student**



Adipose study – Methylome in Colorectal Cancer (CRC) – collaboration with Bob Brown ICR

Aim

To describe the DNA methylation profile of human adipose tissue

To identify differences in the pattern of gene methylation between...

Low and high BMI CRC patients.

CRC patients and non-cancer patients.

Low and high BMI normal individuals.

Method

Quantitative analysis of DNA methylation levels at 244,000 loci from across the human genome.

Targeting regions associated with genes and their transcriptional regulation (Promoters, enhancers, etc.)

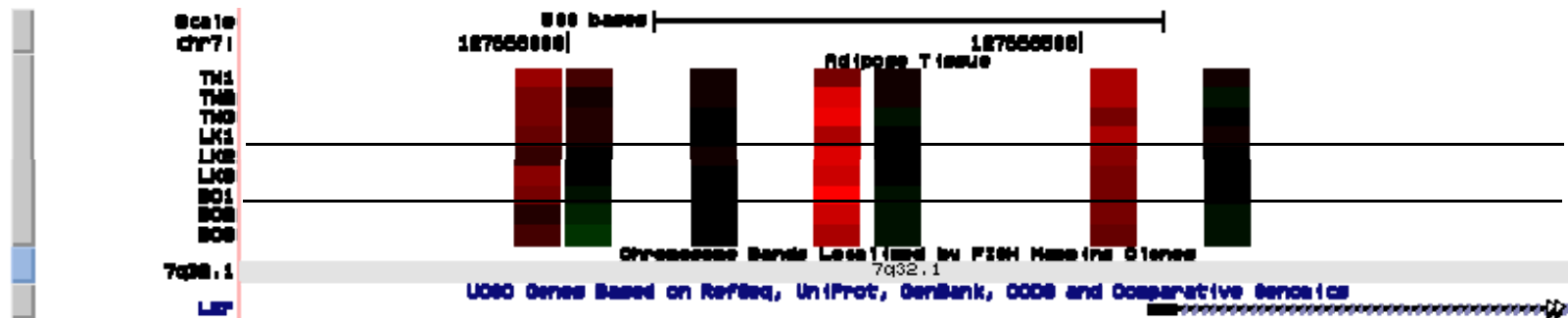
Analysis of visceral fat samples from patients with CRC.

Samples collected during surgery from fat deposits nearest to but distinct from tumour.

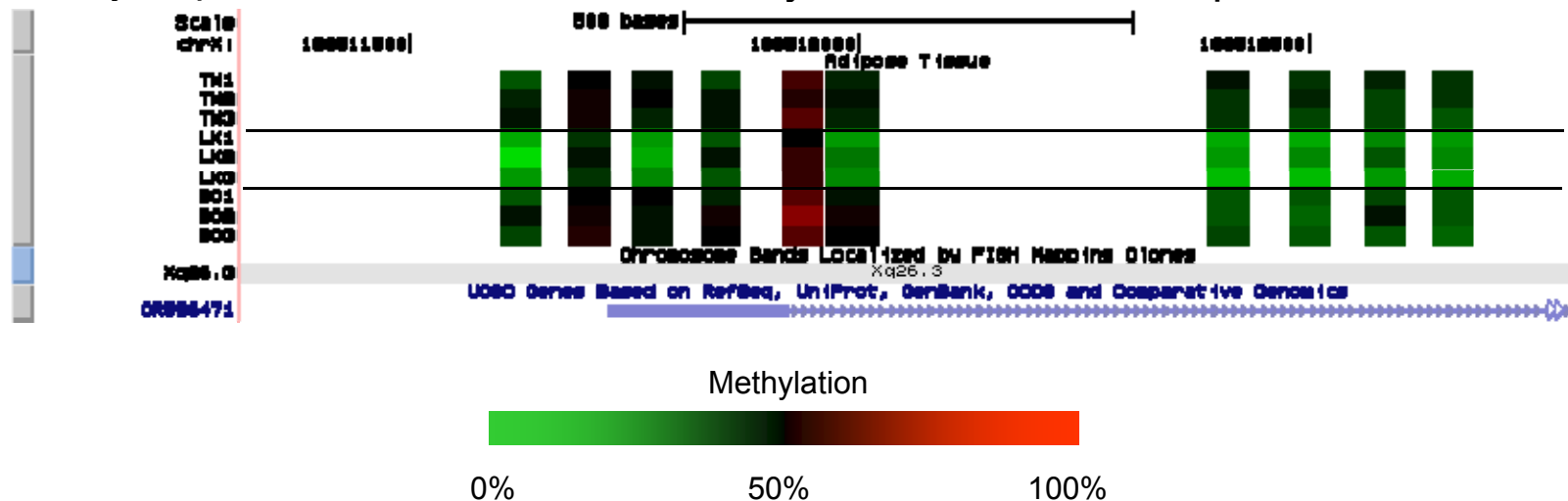
Anton Parker, Rob Howell

Example outputs

LEP – Gene encoding LEPTIN protein, a protein that is secreted by white adipocytes, and which plays a major role in the regulation of body weight, shows expectedly consistent methylation between samples.



mir424 – Encoding mircoRNA 424, an RNA molecule that acts to suppress expression of cell cycle proteins shows variable methylation between samples.

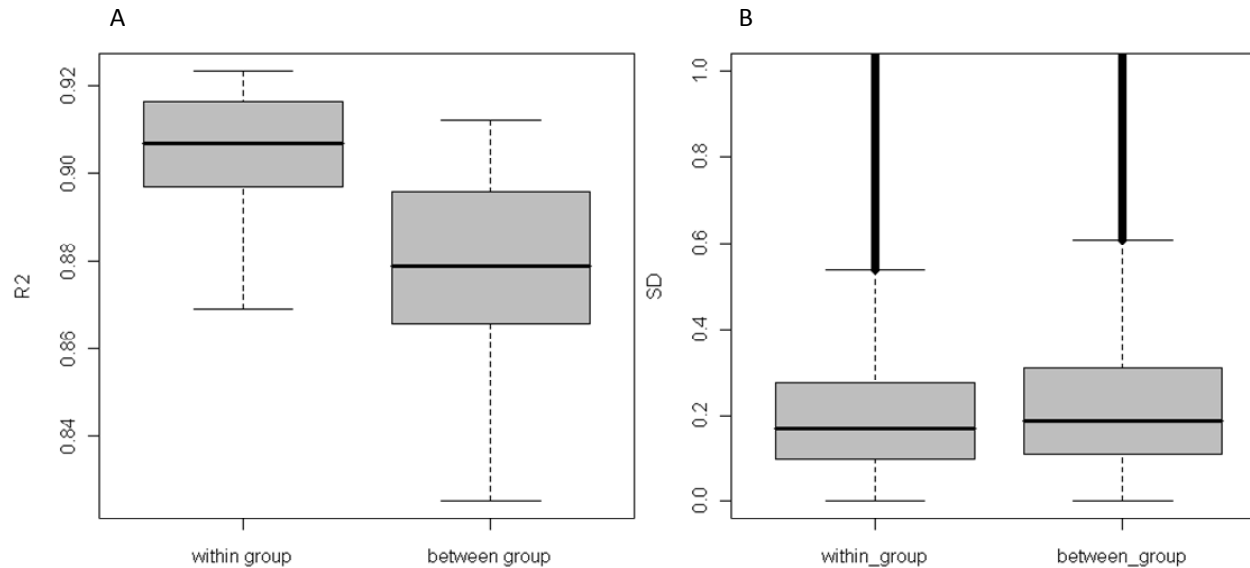


Pilot study

Samples from three separate deposits analysed for each of three patients to estimate inter patient versus variability and allow sample size to be calculated for larger study.

Results

The variation within patients is lower than the variation between patients.



The reproducibility was estimated using R square between the samples.

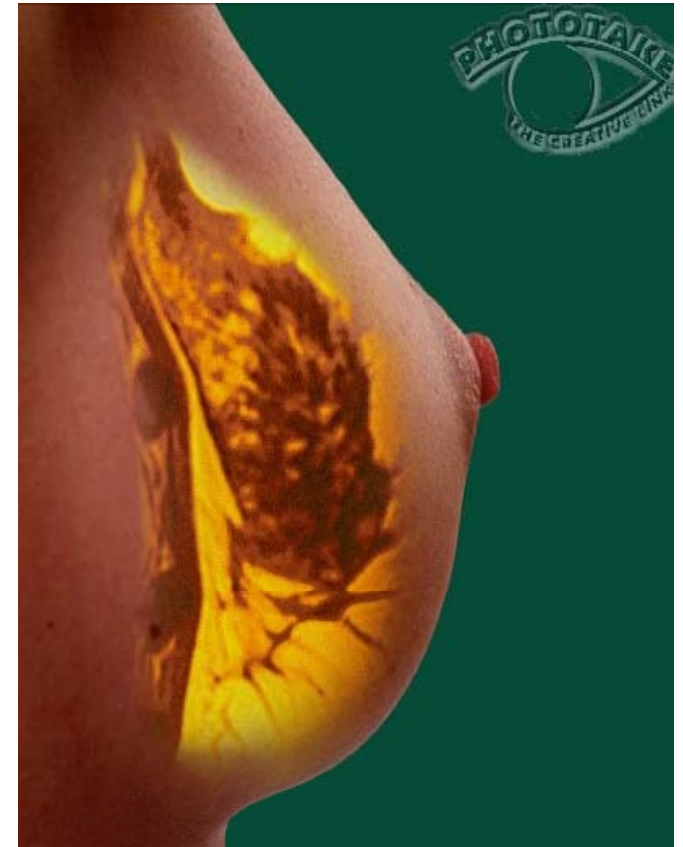
The higher R square indicates the higher consistency of the arrays.

R square within the samples are higher than those between the samples

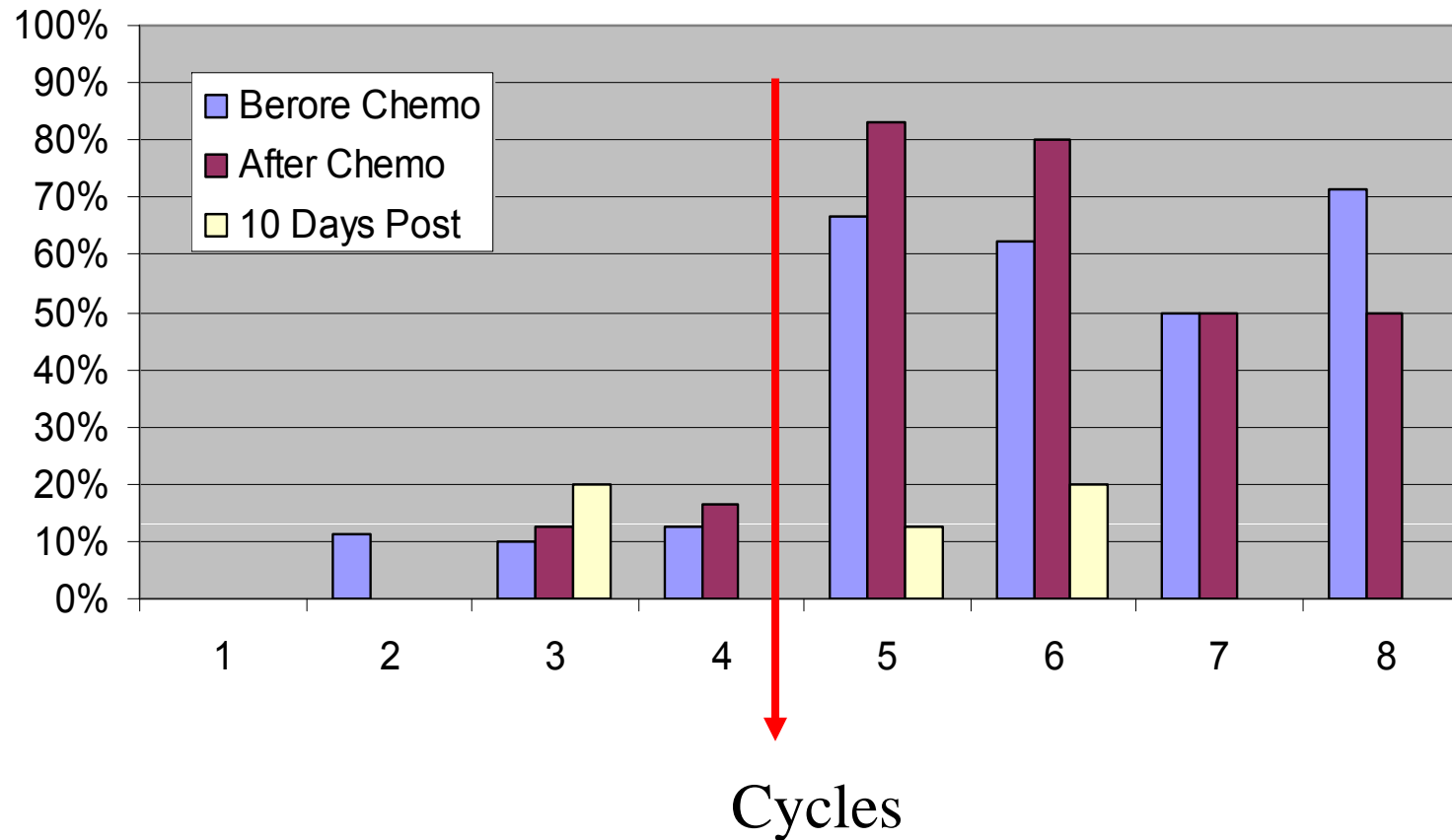
The standard deviation within the samples and between the samples are also estimated

Breast Cancer and Glucose Tolerance

- 26 women, age 57 +/- 13.6 years
- 6 cycles
Fluorouracil, Epirubicin,
Cyclophosphamide (FEC) X4 and/or
Docitaxel X2 or 6 cycles of FEC
- **Dexamethasone** 8mg PO immediately
before FEC
- **Dexamethasone** 8mg PO 24 hours, 12
hours and immediately before Docitaxel



Combined FEC/Docetaxel and Hyperglycemia (>7.8 mmol/l)
Cycles 1-4 FEC, 5-8 Docetaxel



Hickish T et al JNCI 2009

Breast Cancer and Glucose Tolerance

Acute hyperglycaemia is associated with:

- Osmotic symptoms
- Hyperinsulinaemia (a growth factor)
- Impaired immune function
- Vasodilation
- **Alteration of the effectiveness of chemotherapy?**

- **Study extended – fasting prechemo, measurement of insulin, IGF1**

EXERCISE CLASSES!



The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust is delighted to have been able to develop an exercise class for cancer patients in conjunction with the adjacent Village Hotel & Leisure facility.

We have organised a series of weekly classes for patients who have been undergoing treatment in our Oncology Department.

There is good evidence that regular exercise helps prevent the recurrence of certain types of cancer and we are keen to make access to this as easy as possible.

You will be in a class with patients who have experienced similar diagnoses and treatment.

Venue:

The Village Hotel
Thursdays at 11pm from 1st March

Cost:

£2 per session
(payable to the Village)

Contact numbers:

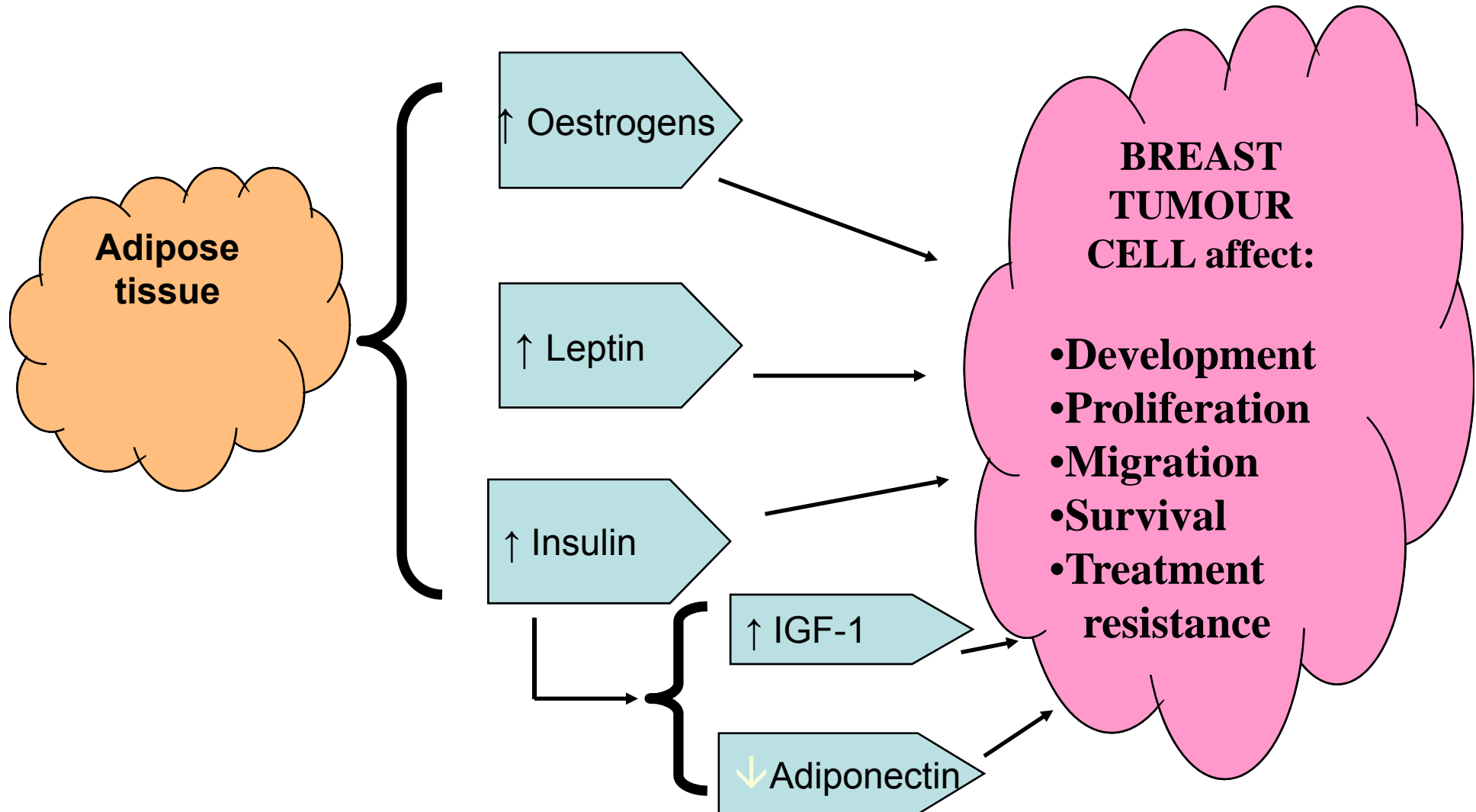
Oncology Dept - 01202 704773
Village Hotel - 01202 416111

★ Please note - membership of the ★ Village Hotel complex is not required



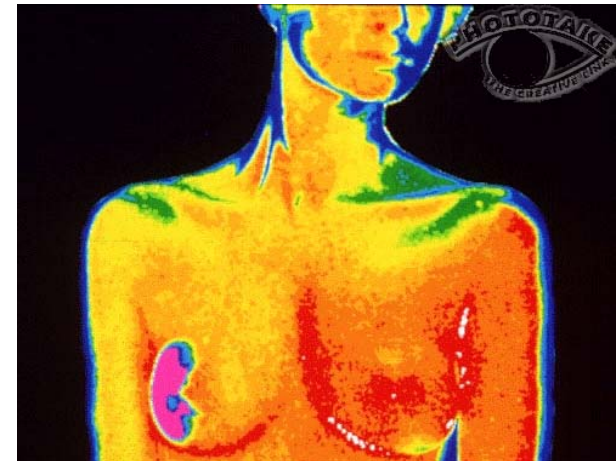
Any questions?

Association between adiposity and breast cancer

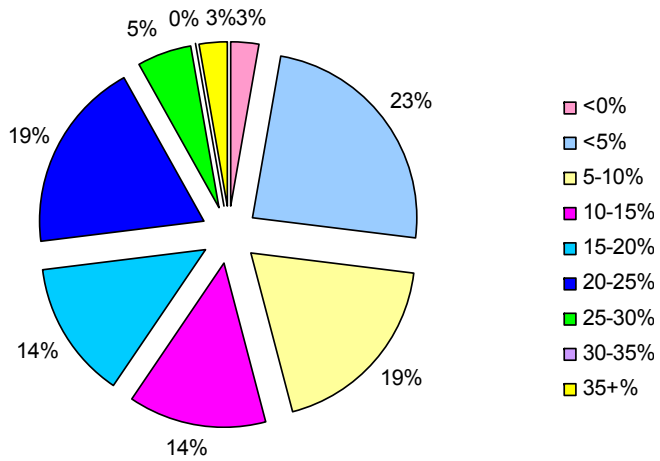


Breast Cancer and Glucose Tolerance

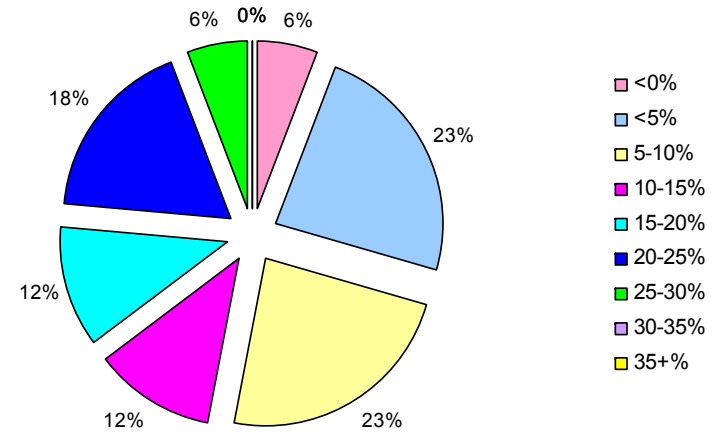
- Non-diabetic women with breast cancer
- Adjuvant chemotherapy
- Blood glucose levels prior to and at the end of each infusion of chemotherapy
- WCC on day 10



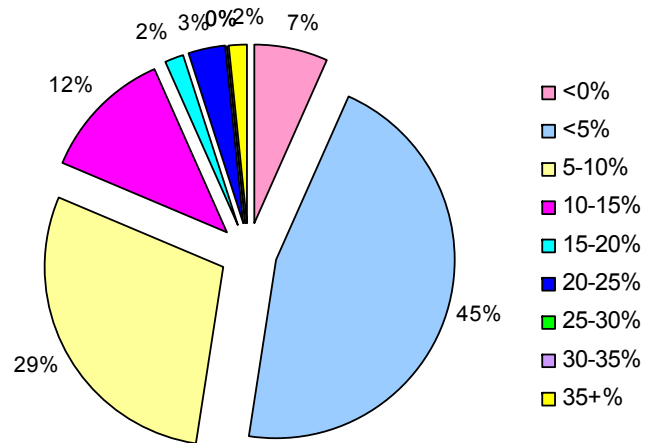
Pre-menopausal weight gain on Tamoxifen n=37



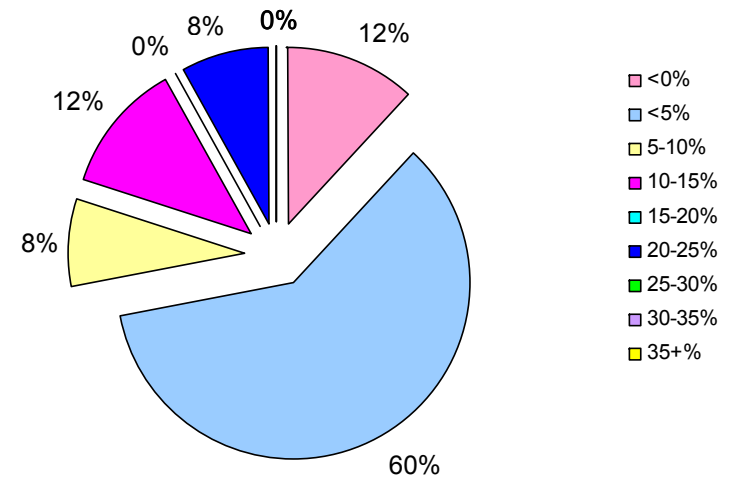
Pre-menopausal weight gain on Zoladex n=17



Post-Menopausal weight gain on Tamoxifen n=59



Post-Menopausal weight gain on Aromatase Inhibitors n=25



[THE BRAIN]

COMMAND CENTER

The human brain regulates weight by integrating information about the body's energy needs and the status of its stores, then initiating changes in behavior and energy processing in response. Specialized brain areas stimulate feelings of appetite or satiety to cause more energy in the form of food to be taken in or to terminate a meal. Over time, the brain can also raise or lower the body's overall energy use and reallocate energy away from systems, such as reproduction, that are not essential for short-term survival.

INFORMATION →

STORED ENERGY STATUS

- Circulating leptin, a hormone generated by fat cells, indicates how much fat they contain

METABOLIC STATUS

- Circulating glucose represents energy immediately available to cells
- Various indicators of liver activity signal that ingested energy is being processed

FEEDING STATUS

- Neural and chemical signals from the gut indicate whether digestive organs are full of food

→ RESPONSES

ALTER BODY'S ENERGY INTAKE

- Direct meal timing and size through appetite and satiety signals

ALTER BODY'S ENERGY USE

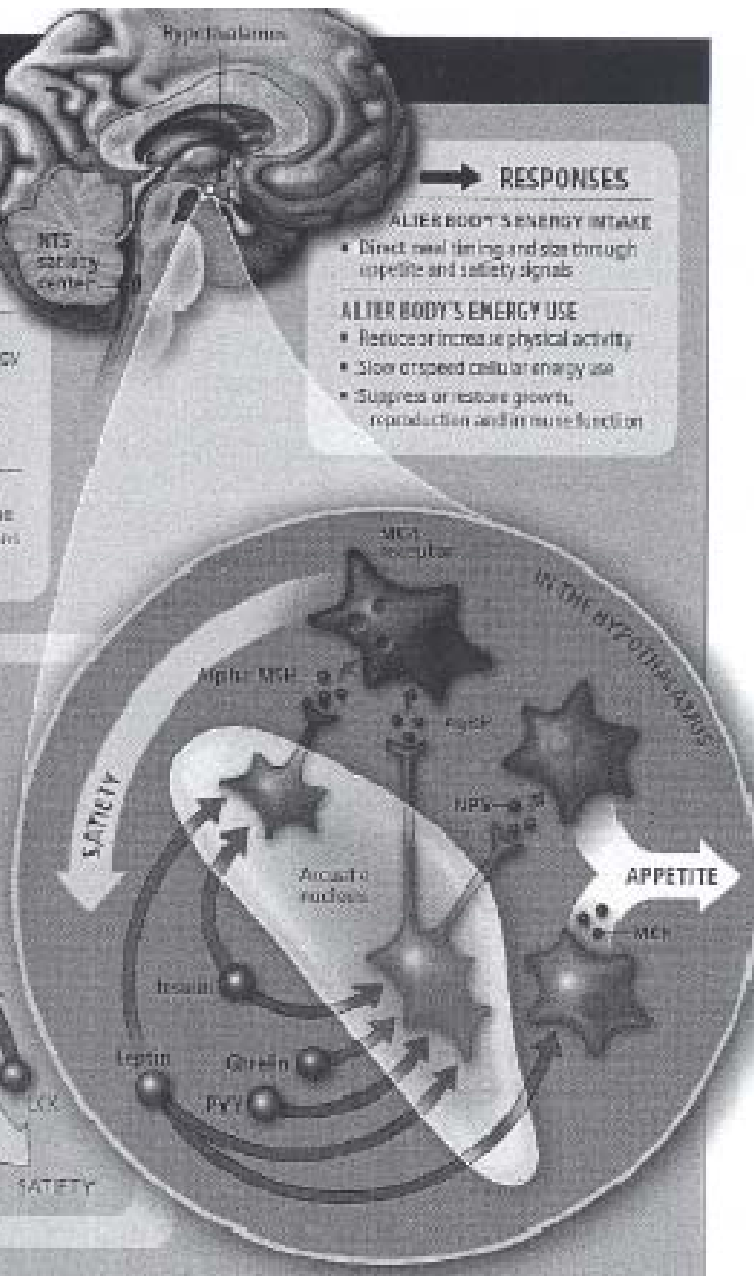
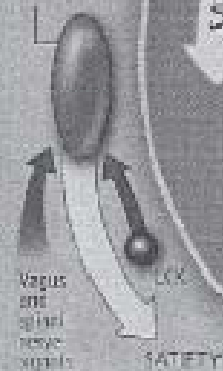
- Reduce or increase physical activity
- Slow or speed cellular energy use
- Suppress or restore growth, reproduction and immune function

APPETITE CONTROL

In the arcuate nucleus (ARC) of the hypothalamus (far right), indicators of energy and feeding status in the form of gut peptides such as ghrelin and PYY, and hormones including leptin and insulin, act upon groups of neurons associated with appetite (brown) or satiety (blue). Each substance either stimulates (green arrows) or dampens (red arrows) the neurons' responses. When stimulated, the ARC cells release peptides such as NPY, AgRP and alpha-MSH, which act on a second set of hypothalamic neurons that induce appetite or satiety. Leptin and insulin act through both types of cells simultaneously to promote satiety while suppressing appetite. Nerve signals and the gut peptide cholecystokinin (CCK) also communicate feeding status directly to the nucleus tractus solitarius (NTS), a satiety center (right) in the brain stem.

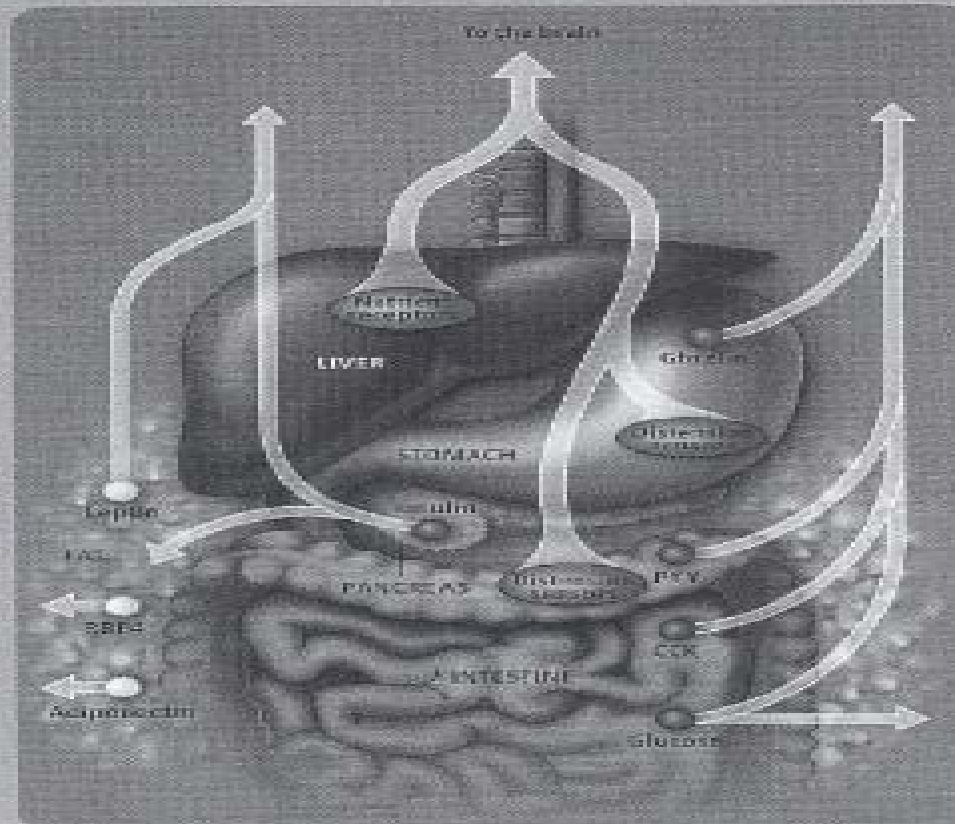
IN THE BRAIN STEM

NTS satiety center



MIXED MESSAGES

Important signals that stimulate energy-regulating responses by the brain and tissues of the body emanate from digestive organs and from fat itself. They constitute both short-term indicators of the body's feeding status, such as nerve impulses and secreted peptides generated just before and after meals, as well as longer-term information about the status of the body's stored energy. In addition to leptin, which reports body-fat levels to the brain, fat cells secrete nearly a dozen other hormones—collectively known as adipokines. At least two of these directly alter tissue responses to insulin, which regulates how much glucose cells take in and use as fuel.



EMPTY STOMACH

- Ghrelin is produced by glands in the stomach 20 to 30 minutes before eating. The trigger for its release is unclear, but ghrelin may signal the stomach's readiness for a meal to the brain.

FULL OF FOOD

- Stomach and intestinal distension is transmitted via spinal and vagus nerves to the brain.
- Nutrient receptors in the liver also send neural signals, indicating that ingested food is being broken down.
- Circulating levels of insulin, secreted from the pancreas, and glucose, derived from ingested food, reflect feeding status and readily available energy.
- Cholecystokinin (CCK) and PYY are peptides manufactured by the intestine and secreted into the bloodstream after a meal.

STORED ENERGY

- Leptin is manufactured by adipose tissue in amounts proportionate to the fat it contains.
- Secreted fat-binding protein-4 (FABP4) also rises with fat levels and reduces other tissues' responsiveness to insulin.
- Adiponectin enhances cellular responses to glucose and insulin, but its adipose levels fall in obesity.

FTO Gene

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

Science 2007

Obese do worse: Why?

- Suboptimal treatment dosing -
- ?Link through metabolism / diabetic tendency

Breast Cancer and Diabetes

- Diabetes is associated with increased risk of breast cancer¹
- Within 5 year mortality in diabetic women with breast cancer is increased by 40%²
- 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 resistance³

¹Int J Cancer 2007; 121:856, ²Breast Cancer Res Treat 2007, July 21st [Epub ahead of print], ³BMJ 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**

What next?

- ‘Total therapy’ – life style factors and interventions
- Research Programme – translational and clinical studies
- Centre for Cancer and Metabolism – physiological, behavioural/psychological, genetic parameters

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

Obese and diabetics do worse: Why?

- Treatment related?
- Perturbed energy balance?

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

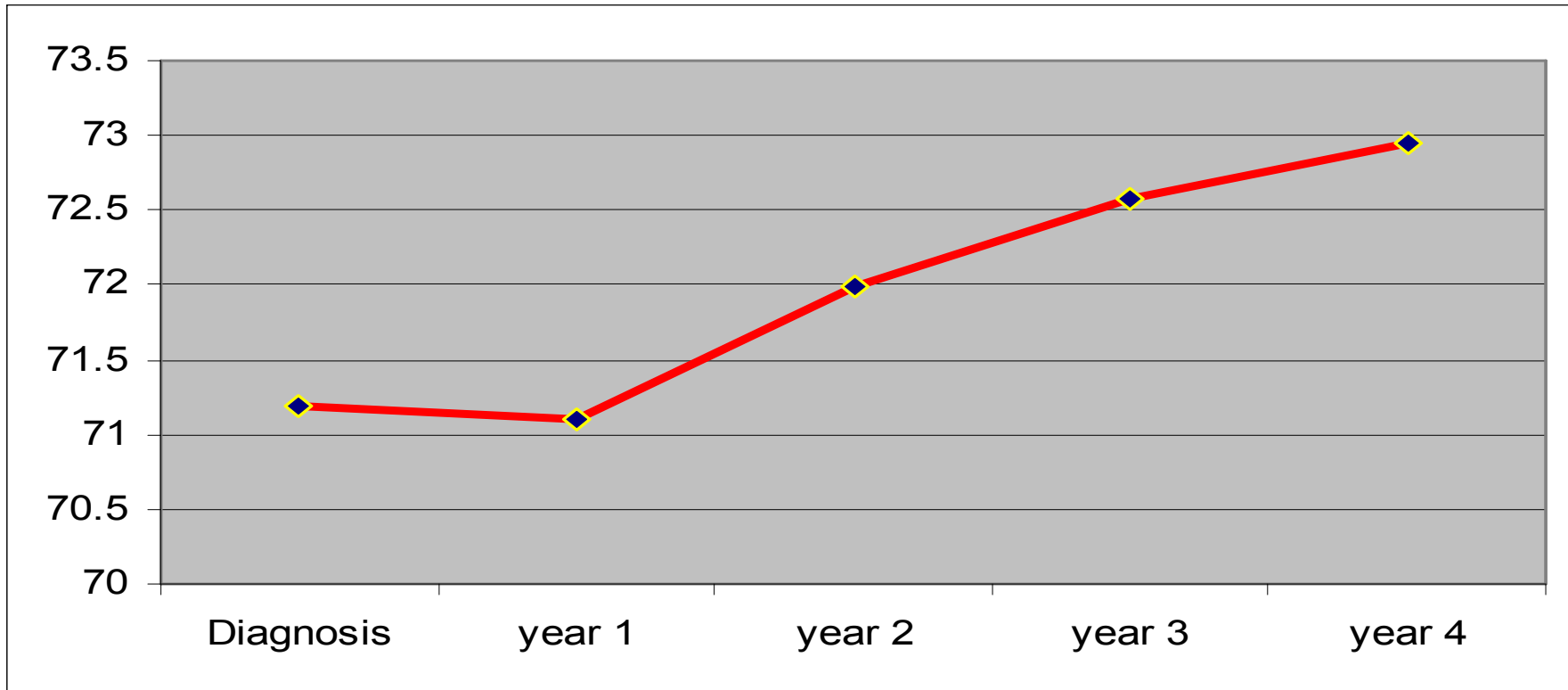
- **Explored factors: treatment and lifestyle**

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**

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

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

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Science 2007

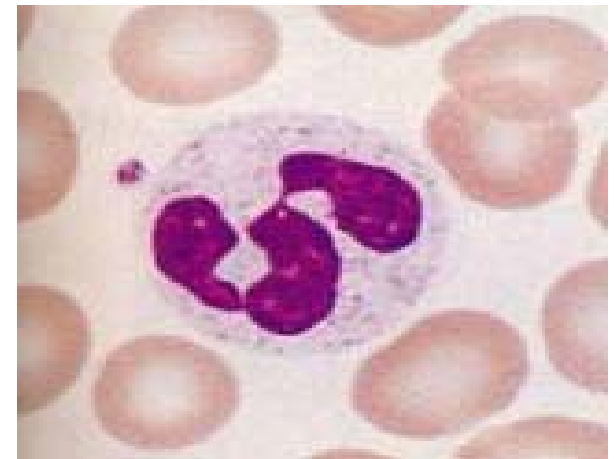
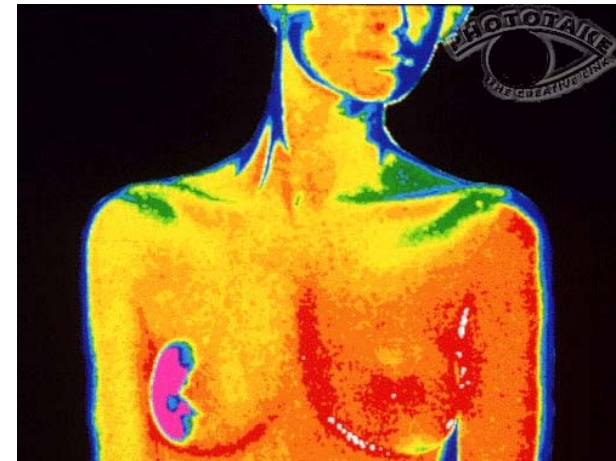
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Breast Cancer and Glucose Tolerance

- 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

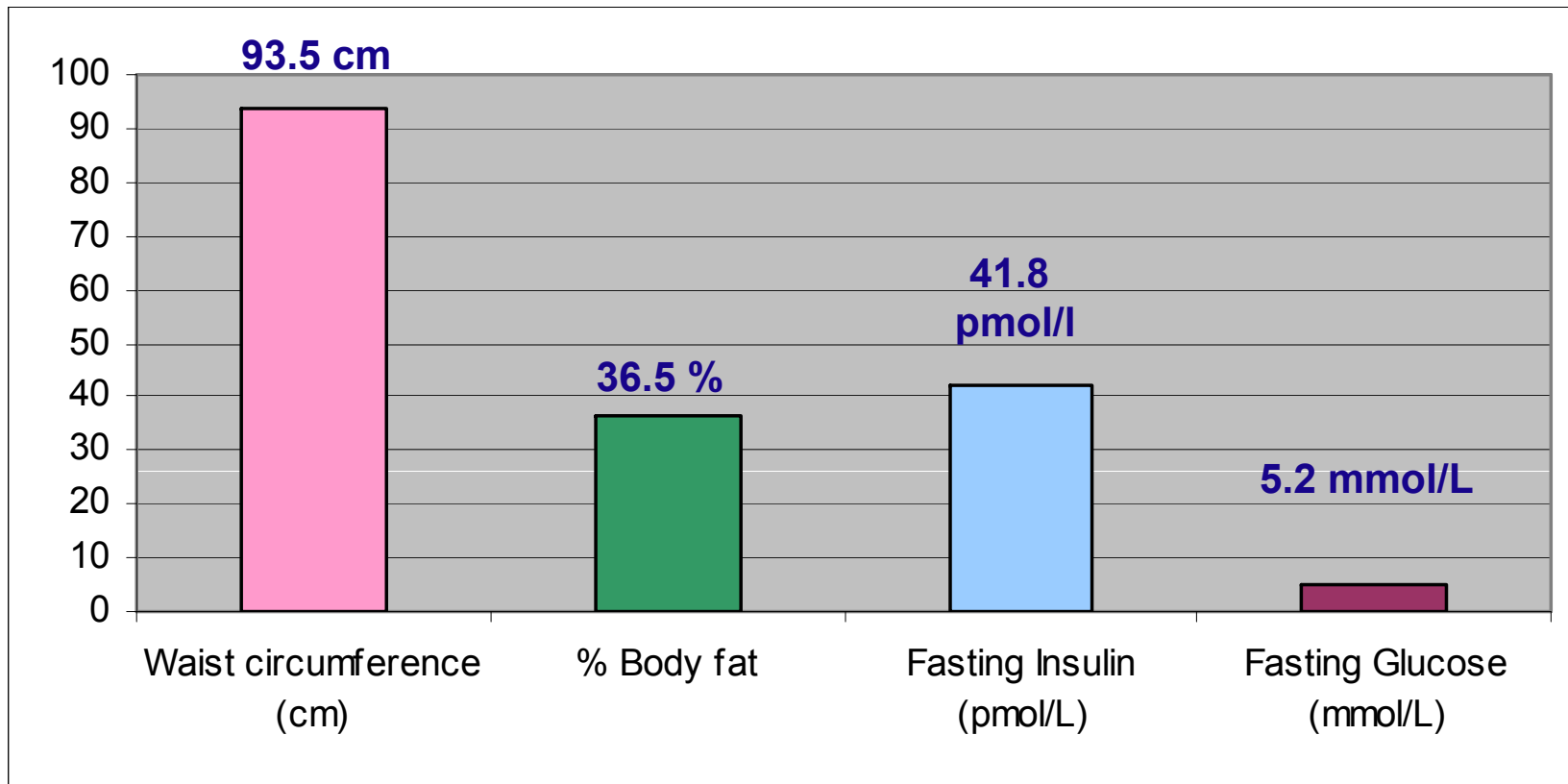
- Understanding cancer cells...DNA, RNA and proteins
- Designing new drugs

Prevention by removing lifestyle risks

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

Getting the basics right

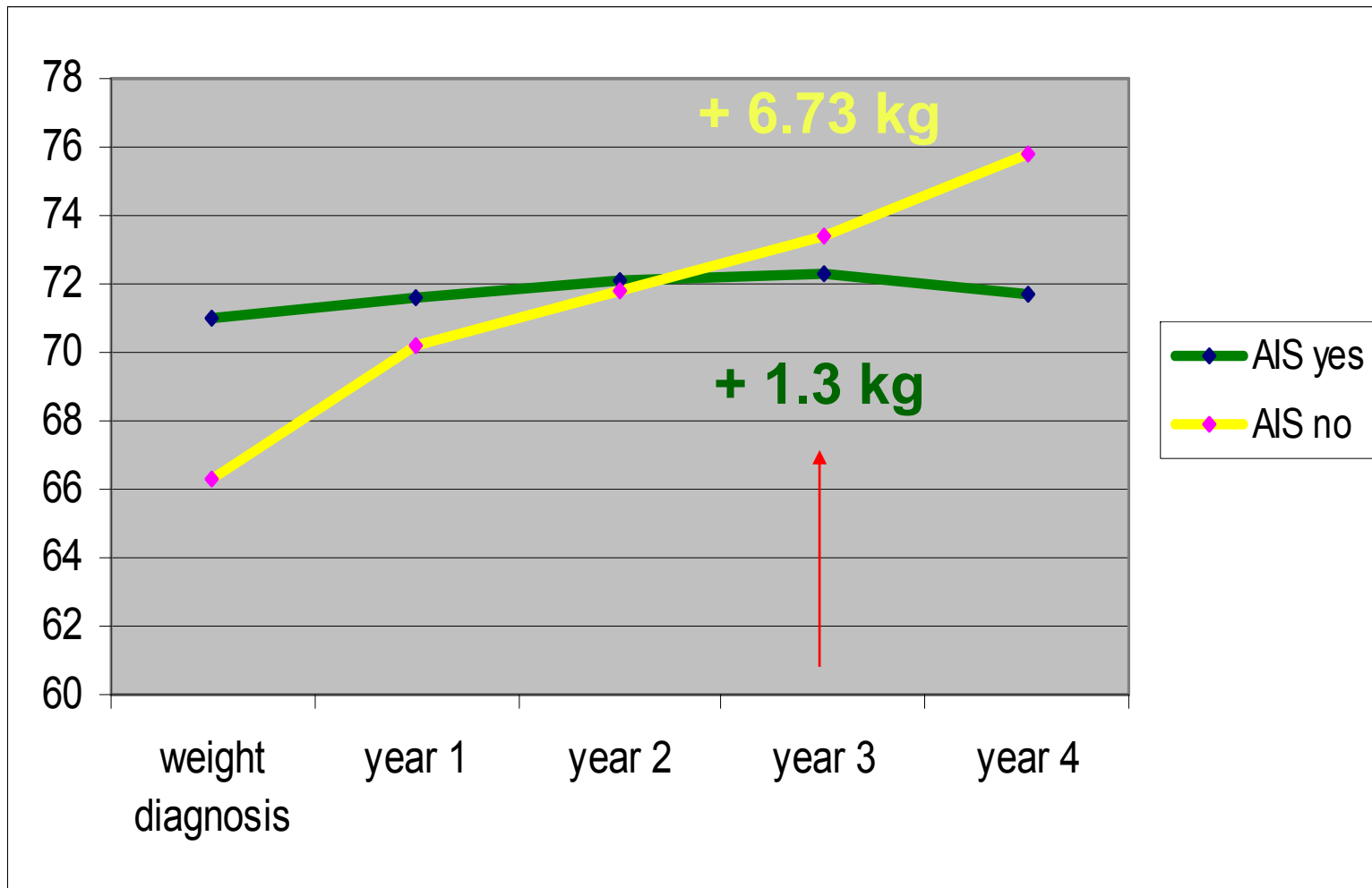
- **Organisational**
 - Cancer Plan
 - 'Waiting times' agenda...levers for change
 - Cancer Networks.....Dorset CN
 - Equity of access, equity of quality
 - Multi disciplinary teams within hospitals
 - Tumour site specific groups across Network
 - Peer Review...Manual of Cancer Standards
 - NICE
 - Research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



Not associated with:

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

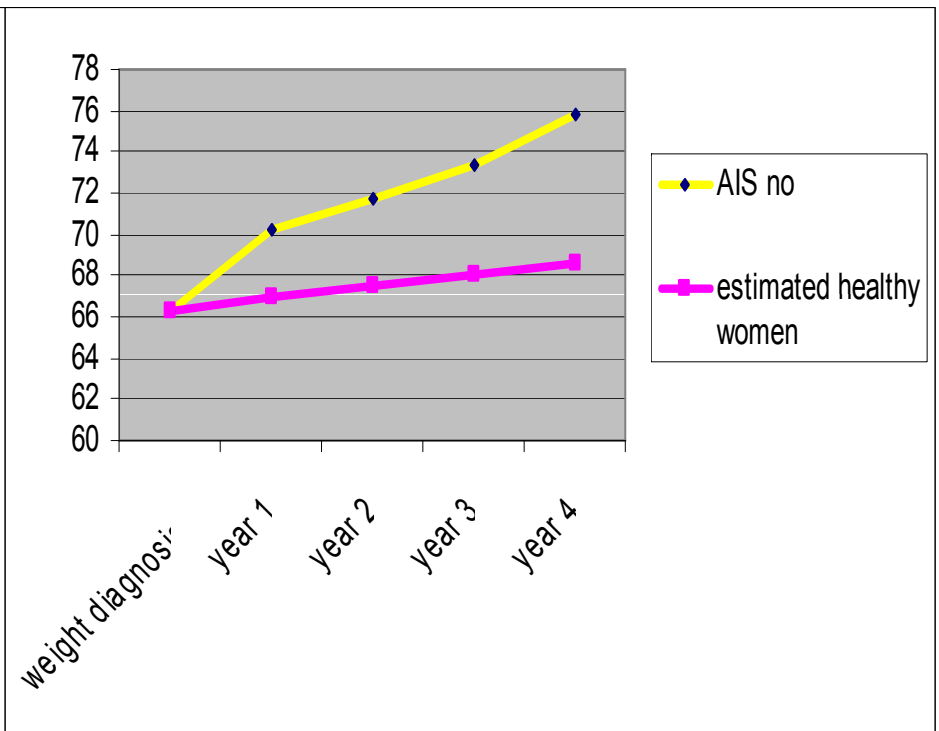
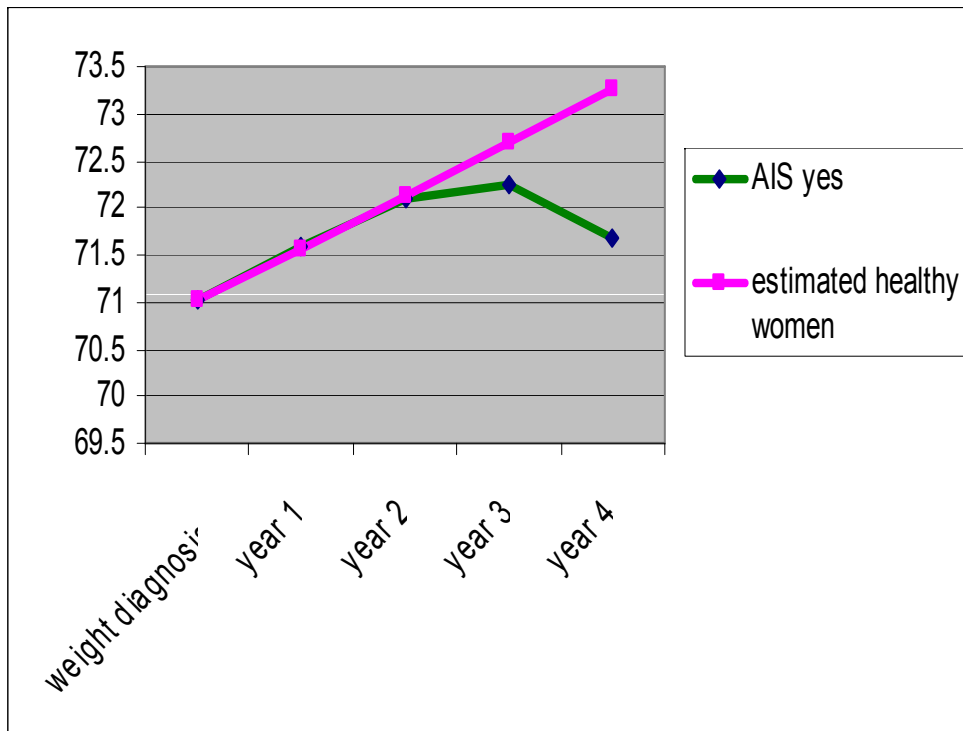
Aromatase Inhibitors



Compared with cohort of healthy women

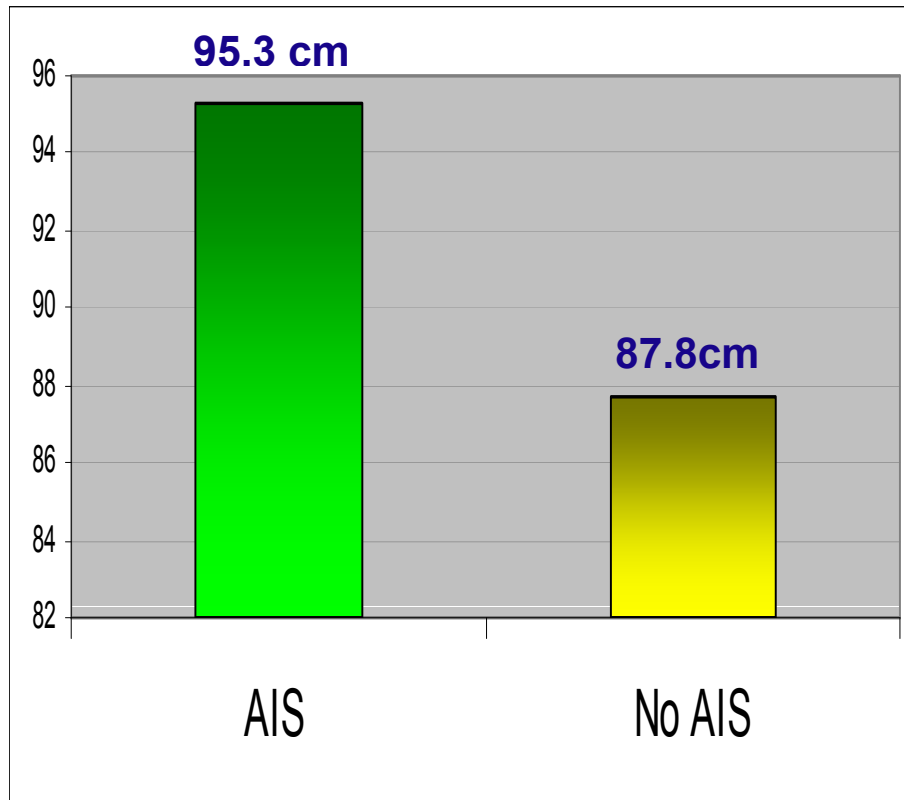
Aromatase Inhibitors

No Aromatase Inhibitors

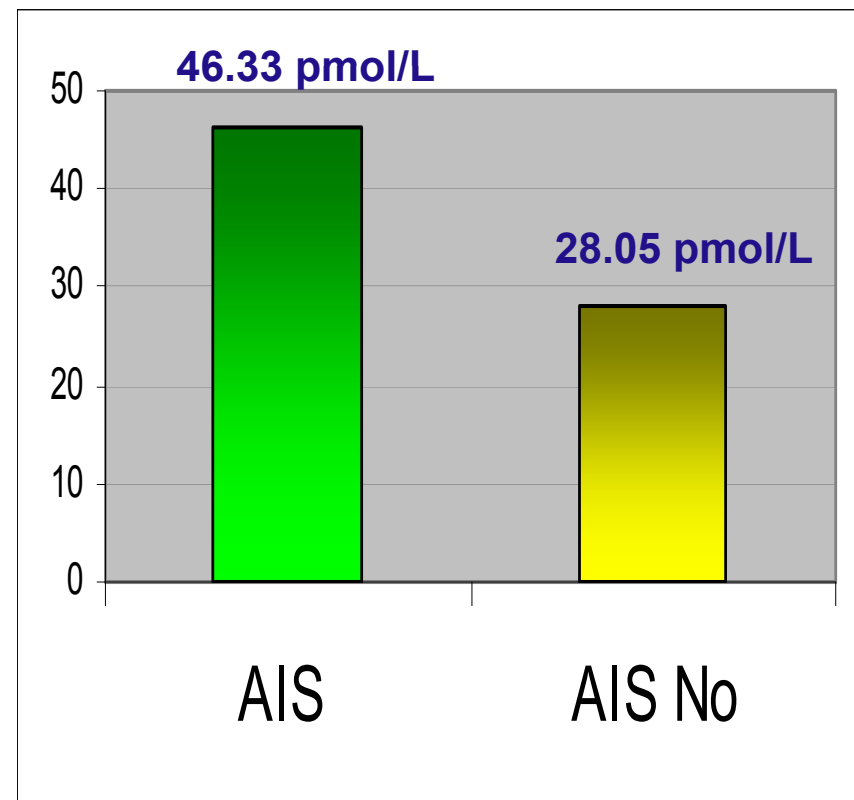


Aromatase Inhibitors

Waist circumference



Fasting insulin levels



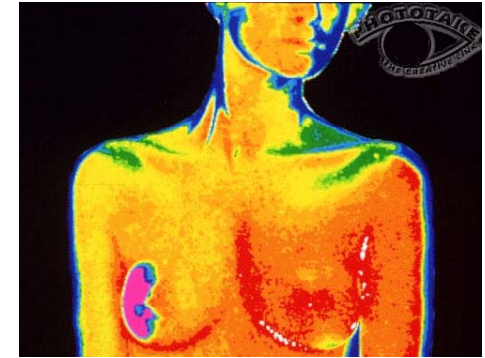
Barberia A et al 2009 unpublished

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



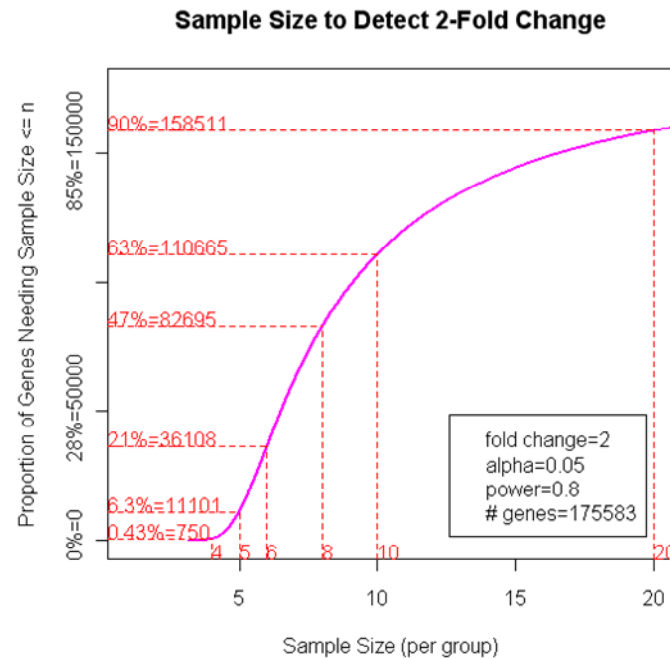
Breast Cancer



- **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?

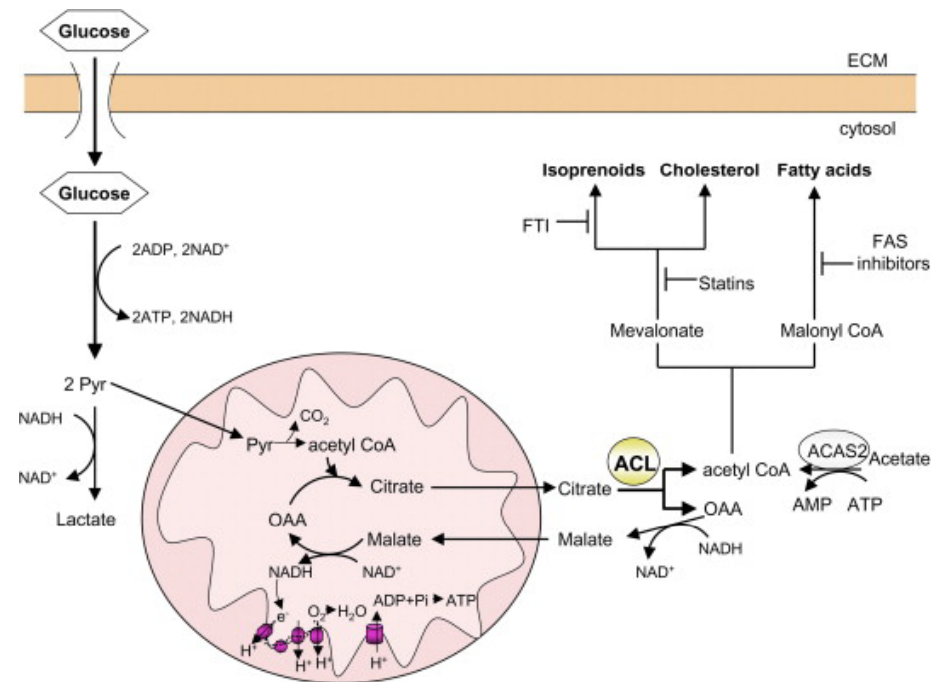
Sample size

Assuming, expected power 0.8, significance level is 0.05, fold change we want to detect between two groups is 2, and using the standard deviation of each gene between patients from the pilot study.



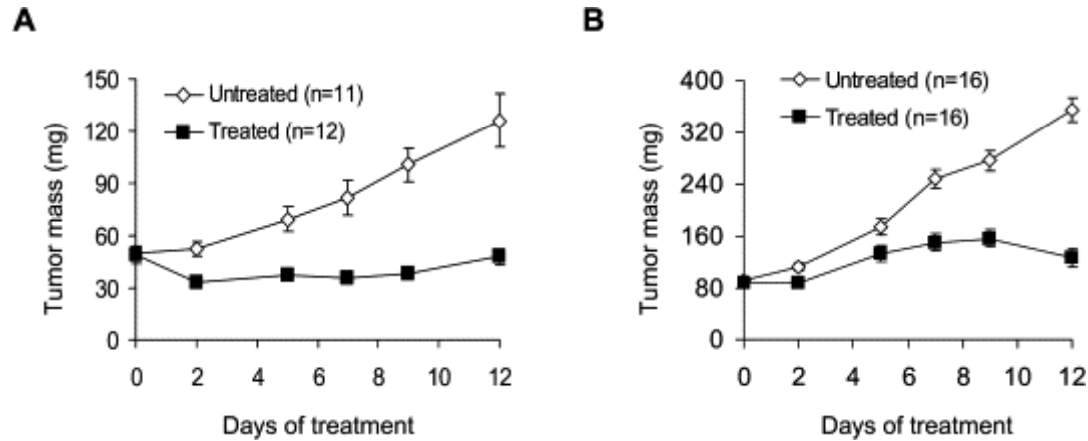
If each patient has three replicates,
4 patients for each group could detect 750 loci with at least 2 fold changes
between two groups,
5 patients for each group increases this to 11101 loci.

ATP citrate lyase regulates the flow of glucose carbons to cytosolic acetyl-CoA during glucose catabolism



Georgia Hatzivassiliou *et al* Cancer Cell 2005

Pharmacological inhibition ATP citrate lyase (ACL)



Inhibition of tumor growth by intraperitoneal administration of SB-204990 in nude mice carrying xenografts of mouse pancreatic ductal cell lines bearing oncogenic *K-rasG12D* alleles. Tumors were established in athymic nude female mice by subcutaneous injection of the indicated cell lines. Cohorts of mice with comparable rates of tumor growth were divided randomly into untreated and SB-204990-treated groups (day 0) and treated by i.p. injection of SB-204990 at a dose of 350 $\mu\text{mol/kg/day}$ (135 mg/kg/day) once daily for 12 days. Graphed is the mean tumor mass \pm SEM. **Georgia Hatzivassiliou et al Cancer Cell 2005**